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BODY FLUID METABOLISM IN THE RAT

A Computer Simulation

by

Robert Anthony St. John Evans

Submitted in fulfilment of the requirements  
for the Degree of Doctor of Philosophy

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## ABSTRACT

### Introduction

Toates and Oatley (1970) presented a computer simulation of rat body fluid dynamics. Whilst their two-compartment (intracellular and extracellular) model was a significant contribution, it does not adequately represent cardiovascular, renal or hormonal aspects of water metabolism.

### Summary

Two models are presented. The simpler model ('small rat') was designed to meet educational criteria, whilst the more complex model ('large rat') is more research-oriented. Both supercede existing models, but the large rat is the more detailed representation. Both are three-compartment models- intracellular, interstitial and vascular. The cardiovascular system is well represented; this has permitted the realistic simulation of many renal, neuronal and endocrine systems important to water homeostasis. Many other related systems are also described, such as the gastro-intestinal tract, energy balance, insensible water loss and electrolyte metabolism in each of the body compartments.

The inclusion of such systems has permitted analyses of the 'volemic' (extracellular) drinking stimuli, and their interactions with other stimuli. The concept of redundancy in drinking stimuli is examined, and a new theory presented that permits its inclusion in current drinking models.

The functional significance of central osmoreceptor siting is discussed, in the light of simulations of fluid absorption dynamics following drinking. Simulations of drinking responses following deprivation are studied. The results indicate an explanation for 'voluntary dehydration', in which water-deprived rats do not restore fluid balance to pre-deprivation levels when subsequently offered water.

The inclusion of 'peripheral' drinking stimuli in the 'small rat' has enabled an analysis of such phenomena as sham drinking.

The nature of the intracellular stimulus to thirst is examined, and a new energy-based theory is presented, which promises to resolve many apparent paradoxes.

Finally, potential improvements and future developments are discussed.



### Acknowledgements

First and foremost, I would like to thank Dr. Fred Toates for his guidance and friendship. I may not always agree with the former, but I know I will always appreciate the latter. Also, I would like to thank Maria, marrying whom was the best thing I have done in the last five years. Finally, I would like to thank my parents, whose kindness and help has been of great significance. I dedicate this to all these people.

'I think also that great harm is caused by too wide a separation of the disciplines which work toward the perfection of each individual art... The result is that men... take up one part only. They leave aside things which point towards, and are inseparable from, that end; and as a result, they never accomplish anything outstanding. They never attain their proposed goal, but constantly fall short of the true essence of the art.'

Andreas Vesalius, 'De Fabrica Humani Corporis', 1543.  
Transl. Clendening, (1942).

'What we call the beginning is often the end  
And to make an end is to make a beginning.'

T.S. Eliot, 'Little Gidding'.

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SECTION 1- INTRODUCTORY DISCUSSIONIntroduction

This section aims to show that the use of computer-based models as an aid to understanding complex systems is part of a natural process dating back several hundred years. Far from enjoying a parasitic existence, feeding on the respectable scientific pursuit of 'experimentation', computer simulations represent a new technique for fulfilling the requirements of Bacon's equally important, but frequently ignored, second tenet of the inductive method. This was that having amassed a corpus of data, one should analyse it, to provide further hypotheses; what Bacon termed 'gradual inductions' (Blake, Ducasse and Madden, 1960).

Analogies used for hypothesis development have always tended to be related to the prevailing technology. In addition, the progress made in scientific understanding has necessitated the use of increasingly advanced techniques for hypothesis formation. The computer is the most powerful technique available.

The section also incorporates a discussion of simulations relevant to the current project. This includes a historical study of relevant cardiovascular studies, as well as prior feeding and drinking simulations. No review of thirst studies generally is offered, as this subject has been completely and skilfully covered by recent publications (e.g. Fitzsimons, 1979; Rolls and Rolls, 1982). An additional review here is considered unnecessary.

The Section closes with a discussion of the failings of models so far developed, and the requirements considered necessary in a future model.

CHAPTER 1Introduction

The aim of science is to understand why nature behaves as it does. When considering animal (and human) behaviour, most would agree that it arises as a consequence of something that is happening within the subject, some internal events that are presently hidden from view.

There are various ways of describing such internal events. Some are popular, but can be deceptive due to their inherent circularity. An example of this would be to state that mothers look after their offspring because of the maternal instinct. At first sight, such an hypothesis may sound appealing. However, the circularity immediately becomes apparent when one attempts to define maternal instinct. It can only be expressed in terms of the very behaviour so recently 'explained' by invoking the concept of maternal instinct.

One can attempt to break this circularity of argument by basing the explanation of a behaviour pattern on various theoretical constructions. Thus for example, one can attempt to explain certain aspects of memory by constructing diagrams with boxes, labelled 'short term memory' and 'long term memory', etc. According to such a view, the aim is to formulate a truly 'structural' model of the mechanisms underlying behaviour, the logic of which can account for its apparent irrationalities.

This approach has some merits. If one regards the magnitude of rigour as being least in the case of verbal

theorising, and greatest in the case of systems-based or mathematical expressions, then such models do represent something of a 'half-way house'. They are also relatively easy to communicate to other members of the academic profession. However, their apparent rigour may be deceptive, masking (say) fundamental misinterpretations of physical laws. As with most of the disadvantages, this is a consequence of the fact that such models have no depth of explanation. In a reductionist sense, the blocks comprising the model are at the same level as the phenomenon being investigated. Because of this, any properties that emerge can only do so as a consequence of interactions at that level. However, it is quite feasible that significant emergent properties can arise from interactions at a lower, more reductionist or 'atomistic' level. These obviously cannot be created or predicted by the single-level model. Thus when the behavioural consequences of such a low-level interaction are observed, the single-level model will appear to be disproved, despite it perhaps being a valid representation at that one level. In addition, as is discussed below, creating a model at only one level removes the option of a second technique of validation; the similarity of the model's 'deep structure' to experimentally observed structures. Presently of course, extending a model in depth, in addition to scope, is not always possible. In the case of behavioural simulations for example, the 'building blocks' comprising the relevant behaviour cannot be discerned. Eventually, behavioural patterns will probably be explicable in terms of neurons and their

connections. For the present, however, the nature of the relationships are unknown, and thus one cannot express behaviour in more reductionist terms.

Nevertheless, it is felt that greater consideration should be given to the depth of explanation of models. As Weiskrantz (1973) put it;

"First, we have all too many examples of two logical models starting from quite different, even contradictory, assumptions, and yet fitting the empirical facts equally well. Even in physics one can translate from wave into quantum theories of light. Which theory one chooses turns on matters of preference and aesthetics, or at best on grounds of parsimony where it is not all that easy to calculate degrees of parsimony. The second objection is that it is possible for a structural model to make correct predictions and yet be fundamentally wrong because it ignores the details of internal bodily events." (p.512)

The objections cited by Weiskrantz are essentially due to the fact that such logical models deprive themselves of a major means of validation. For such models can only be tested by checking their predictions against observed events, and as Weiskrantz stated, it is perfectly possible to have two differing models that are indistinguishable in terms of their predictions.

If however, one can construct a model whose logic reflects that of the structures underlying the behaviour in which one is interested, the second means of validation

becomes available. In addition to referring merely to the predictions made by the model, and their similarity to observed behaviour, one can then also refer to the similarity that the prospective model bears to observed structures. Thus, one does not need to rely entirely on such tenets as 'parsimony'; one can also use the more rigorous yardstick of the similarity that the 'building blocks' of the model bear to the physiological and neurophysiological building blocks which are known to create collectively the observed behaviour. Whilst not making Occam's razor redundant, examining the model's constituent components and adopting a more reductionist attitude may provide a somewhat sharper tool.

Francis Bacon stressed that the inductive method does not merely consist of simple enumeration of all data; this by itself does not make science. The method must include a technique for the assimilation and classification of data. By drawing together the common threads that run through our accumulated experience, we can eliminate a progressively larger number of hypotheses, until at last only one remains. In this way, he considered, one would discover the 'form' of the phenomenon studied, its very nature and inner essence. The theory held would then be isomorphic with Nature. (For an excellent description of Bacon's philosophy, see Durant, 1964).

Whilst present philosophical attitudes may have considerably advanced since Bacon's day, his concept of unifying Nature by drawing together the threads, making order out of the chaos, is a fundamental aim of all

theories.

Theories are merely clothes shaped as best we know how to fit the body of facts presently at our disposal. To extend the analogy further, it would follow that no theory can ever actually become the aspect of Nature studied; they are only mental constructs, and can only reflect its shape, enjoying parallel existences.

How is a theory expressed and communicated from one person to another? As all theories have to be created via the medium of the human mind, they can all be regarded ultimately as mental constructs. It is only in the form of their external representations that they differ. By analogy with John Locke's (Locke, 1690) concept of visual perception, the written theory can be regarded as the distal stimulus; they are of no significance until converted by our mental faculties to an internal representation, the proximal stimulus.

Theories differ in the form of their external representation. The majority are 'verbal', where words are used to express the constructs underlying a behaviour and their inter-relationships. Some are mathematical, where the relationships are expressed as a series of equations. These have the advantages of being both concise and specific, but suffer from the disadvantage of having a restricted audience; mathematics is not as widely spoken as English. In addition they may not always have the sort of explanatory depth one would like, being little more than elegant descriptions of the original data. An example of this is the 'Wood's type' function fitted to the milk yield of the dairy

cow throughout her lactation cycle (Wood,1967).

Computer-based theories tend to fall between these two camps. If properly designed and documented, a theory embodied in a computer program will have the rigour of a mathematical treatment, yet retain a comparative ease of communication. They can be used to represent very complex systems and their interactions, that are beyond the scope of verbal descriptions alone. Considering Bacon's aim of the unification of previously disparate bodies of data, the facility of a computer program to study large systems and their complex interactions (emergent properties) will be of paramount importance in coming years.

The aim of the simulation presented here is to analyse body fluid dynamics, and the interactions that occur between the systems subserving energy and water regulation in the laboratory rat. A modest aim indeed; yet the nature of these interactions has for years defied the many attempts at verbal theorising, leading to a considerable confusion and the acceptance of many apparent paradoxes. It is considered that these are most likely to be resolved by a comprehensive, multidisciplinary, computer-based study. Such an approach may employ a relatively new technique, but the concepts underlying the approach are traditional. The present author sees no difference in aims between verbal, mathematical and computer-based theories. All are representations of Nature. None, if one accepts the Popperian concept of successive theories forming a gradually improved approximation to an unobtainable absolute truth, will ever be truly isomorphic with Nature. None will



actually become the aspect of Nature observed. The only differences are a consequence of the means by which the 'distal stimulus' is represented. However, they do differ in their theoretical rigour. Sagawa (1973) perhaps puts it more succinctly;

"Modeling is one of the fundamental processes in our understanding of Nature. From observations of phenomena we abstract functional relations (causality) among the substantial elements of a system of interest. Whether the abstraction is intuitive or mathematical, it is the first step of modeling. The induced model is then checked against the next observation through a deductive process and, as a result, discarded, revised, or further tested. The model may be very elementary, being a verbal speculation of the cause-and-effect relations among the related elements, or it may be very formal (mathematical) expressions induced from accurate observations and analytical thoughts. Although both types of modeling provide momentum for research, the more quantitative a model is, the more exact becomes the deduction and the testing. For this reason, formal modeling is preferable, and modern computer techniques make it far easier than it was decades ago." (p.1)

These advantages can be put to good use in the subject of drinking and its control, especially following various physiological interventions. A great mass of experimental data has been accumulated over the years, some of which appears inexplicable. It is apparent that verbal theorising

alone cannot offer an adequate explanation, and the only hope is to resort to a systems-based theory. As Booth (1978) wrote;

"I am sceptical of my ability to work out intuitively the implications of my physiological and learning process theory of hunger. I know from experience that I am too stupid to co-ordinate more than two or three definite hypotheses at once without sometimes committing logical fallacies. The attraction of a mechanized synthesis of an explicitly analysed system is that it can release scientific understanding from the limited capacity of the individual human mind." (Booth, 1978; cited by Bray, Booth et al 1978, p.452).

Siebert (1978) discussed the controversy created by the presentation of computer models, and enumerated a number of features desirable in good computer simulations. Such suggestions are to be welcomed, for there are undoubtedly good and bad simulations, as there is good and bad research. Siebert's comments are worth examining in some depth but, briefly, are as shown below. It is to be hoped that the simulation presented here conforms more or less to these strictures.

Firstly, the model should be presented with all equations fully shown, and their dimensional consistency established. Variables should be fully defined.

Secondly, the domain of real time over which the simulation is intended to be valid should be given, together

with justifications for all assumptions made about the system's structure. Relevant papers supporting such assumptions should be cited.

Thirdly, if predicted data are being compared with actual data in order to validate the simulation, then the criteria used to determine goodness of fit should be given.

Finally, Siebert (1978) feels that one should ideally present not one, but two models, each of which can be justified by the scientific literature, but which predict significantly different outcomes of a particular experiment not used in their construction. Thus one model will fail, and the other succeed, or both will fail. In either case, the use of models as a tool for hypothesis rejection is demonstrated. Whilst agreeing with this, the present author feels that the alternative model need not be one in the simulation sense; it may be a verbal or mathematical treatment.

An oft-overlooked point is that science is a community activity, and a model must be communicable if it is to be considered part of science. A model that can only be comprehended by its creator is undoubtedly destined for a short academic life.

Previous Models of Animal Physiology, Drinking and FeedingHistorical Background of the Subject, and Relevant Physiological Models

Over the years, many attempts have been made to simulate complex systems in a variety of disciplines, and by a variety of techniques. The simulations of specific relevance to the current topic appear to fall into two categories, although of course the boundaries are somewhat arbitrary. The first category is that of the physiological system simulations, usually attempting to unravel cardiovascular or occasionally renal regulation. The vast range of work by Arthur Guyton is representative of this category. Second, there is the more diverse category of simulations whose aim is to analyse behaviour, or at least study systems believed to subserve behaviour. In this category one may place the work of Oatley (1967) and Toates and Oatley (1970).

The physiological simulations appear to have a longer history, especially those pertaining to cardiovascular regulation. The review given here is necessarily brief; for those interested, the subject is dealt with more ably and in greater depth by Sagawa (1973).

Some models pre-date the widespread availability of electronic computers. Thus Lowe (1955) presented an ingenious hydraulic cardiovascular system comprised of floats, valves and endless belts. The predictions were in good agreement with his previous clinical experience (e.g. Lowe, 1953) of various cardiovascular ailments.

By 1960, analogue computers were more generally available, and they seem to have been put to good use. Pace (1960) presented an analogue computer model that simulated water and electrolyte flows between the intracellular and extracellular compartments. This does have the merit of being the first simulation to divide the body into two compartments. However, its treatment of cardiovascular dynamics is scant to say the least, and, without this, one cannot realistically represent renal function nor predict cardiovascular receptor responses. As shall be shown, since this time, many models have continued to gather the interstitial 'fluid' and cardiovascular system into one compartment, termed 'extracellular'. The validity of this convenience shall be questioned later.

In 1963, Fincham presented as his Ph.D thesis an analogue simulation of renal dynamics, including anti-diuretic hormone (ADH) control of fluid reabsorption (Fincham, 1963). This was a great step forward, as it illustrated the capacity of computers to represent complex systems, and showed that the next move must be to analyse the behaviour of the driving force behind the kidney, the cardiovascular system.

For many years, the study of the cardiovascular system appears to have concentrated on fine details of its structure. Despite pioneering work by Starling (Frank-Starling law of the heart, Starling's capillary equilibrium), the study of the system's dynamics remained in the doldrums until the 1950s. A major stimulus to the revival of interest in cardiovascular dynamics was Arthur

Guyton and his colleagues at Jackson, Mississippi. He appears to have always been concerned with this topic (e.g. Guyton, 1948, 1955), and quickly grasped the potential of computers in understanding this complex question. Thus in 1967, he published the first attempt at a complete representation of long-term circulatory regulation. This not only incorporated cardiovascular physiology (the experimental data for which came largely from his own laboratory), but also reasonable representations of renal physiology and trans-capillary flow. He thereby acknowledged for the first time in a simulation the existence of an interstitial fluid compartment, and its contribution towards circulatory dynamics. (Guyton and Coleman, 1967). It also embodied a rudimentary autonomic nervous system.

These systems were extended, and more added, in his comprehensive model of 1972. (Guyton, Coleman and Granger, 1972). This model includes a host of mechanisms involved in body fluid regulation, namely, protein synthesis and its leakage, lymph flow, renal dynamics, a rudimentary thirst and drinking mechanism, ADH, angiotensin, and aldosterone controls, trans-capillary fluid shift, and interstitial fluid pressure effects. Uniquely for its time, the model also incorporated short- and long-term autoregulation of vascular resistance, comprised of stress-relaxation systems, autoregulatory vasodilation or vasoconstriction, and long-term changes in vascularization in response to persistent errors in tissue perfusion pressure. Sagawa (1973) considered these aspects to be "one of the most powerful controls of the circulation". (p.89).

None of these vital regulatory systems that subserve drinking behaviour could be represented by the 'two compartment' type of model presented by Pace (1960) or Toates (1971). Yet to date these are the best available to students of thirst motivation. However, all of the regulatory systems previously discussed are implemented in the larger of the two models to be described in this thesis; the majority are also in the smaller, micro-computer based model.

Given all this, what does Guyton et al's (1972) model not have? In an unusual sense, it too only just avoids being a two-compartment model, as it concentrates on the vascular and interstitial compartments; scant attention is given to intracellular dynamics. The contribution of Guyton and his colleagues in recognising the significance of interstitial dynamics in overall regulatory dynamics is undoubtedly significant. (E.g. Guyton 1963, 1965). However, the inadequacy of their simulation of the intracellular compartment prevents one from studying (say) the effects on water metabolism of starvation, and any interactions between feeding and drinking. In addition, as the emphasis of this model is obviously physiological, no attention is given to the so-called peripheral influences on water intake, such as gut volume or oral metering. Those drinking stimuli that are represented are hindered by the simplicity of the intracellular compartment. As the animal simulated is not required to eat, the treatment given to the gastrointestinal tract generally is rather scant. Finally, the simulation presented by Guyton and his colleagues is that of

the human cardiovascular system; the object of interest in the current context is the laboratory rat, since the vast body of thirst literature is rat-based.

It would be churlish to construe these comments as criticisms of Guyton et al's (1972) simulation. It should be noted that models are always developed with a specific aim in mind. One cannot hope to present a truly generalisable simulation that can represent any aspect of physiology (or Nature generally) merely at the press of a button; such a model would be impossibly large. Thus one has at the outset to define the boundaries of a model, within which are contained the phenomena and subsystems relevant to the aims of that model. Thus it is by no means inevitable that the 'domains' of Guyton's models and the model presented here should overlap. Due to the necessities for creating boundaries around a model's 'domain', one usually finds that models representing aspects of physiological regulation over-simplify any relevant behavioural controls, if they are represented at all. Naturally, this is often a reflection of the range of experience acquired by a simulation's developer. In a similar manner, there is a danger that models of behavioural regulation ride rough-shod over the great mass of relevant physiological systems. This, it is felt, is considerably less defensible. If one accepts a hierarchical structure of science, it is exactly analogous to a biochemist refusing to acknowledge the relevance of physics to his study.

Since Guyton et al (1972), simulations of physiological regulatory systems have increased in both breadth and depth.



Ikeda et al (1979) further developed and extended Guyton et al's (1972) model, placing particular emphasis on acid-base balance. This human model did incorporate an intracellular compartment, but lacked any behavioural controls. Thus the system cannot decide for itself when to drink, and there is little point in feeding it, as there is no energy regulation. It is however, an impressive piece of work.

At the other extreme, models have also been developed to look at the finer details of physiological systems. For example, Lau and Sagawa (1979) studied the contribution of atrial contraction to ventricular filling in considerable depth. Huikeshoven et al (1980) have proceeded to study the special case of the foetal cardiovascular system.

Models of Feeding and Hunger

Models of feeding and hunger can be classified into a number of sub-groups. As in so many cases, this is often a reflection of the question to which the model's author is addressing him or herself. Probably the best overall review of the subject is the volume edited by David Booth (1978), and much of the discussion presented here is derived from this.

Neural Integrative Models

The first category of models places a particular emphasis on the integration of the neural systems subserving feeding regulation. These will, for example, assess the effect of hypothalamic damage (e.g. Hirsch, 1978), or analyse the type of 'reverberatory' circuit that can operate in feeding regulation (Barnwell, 1978).

The work of Tony Ludlow tends to fall into this category of neural integrative models, although it frequently incorporates aspects of feeding behaviour that are normally the preserve of other categories discussed here. Ludlow (1982) presented an elegant theoretical decision-making system based upon known principles of neuronal action. This realistically simulated the patterns of behaviour observed in rats when faced with a choice of activities, and is at least one way in which the individual components of the nervous system could interact to produce recognisable behaviour.

This question of achieving the optimum balance of conflicting behavioural opportunities (e.g. eat, drink or be

merry) has also been addressed by David McFarland and his colleagues at Oxford (e.g. McFarland, 1978). Rather than rely on possible neuronal systems, McFarland uses a somewhat individualistic and interesting technique. He views the internal environment of an animal as giving rise to a system of interacting motivations, which are subject to variations in the animal's behaviour. The state of the internal environment can thus be described in terms of a finite number of physiological state variables, each of which can be represented as an axis of n-dimensional hyperspace (McFarland 1982, p.386). \*

However, the approach posited by McFarland suffers from a difficulty endemic in all decision-making systems attempting to simulate animal behaviour. Because the underlying physiology (i.e. the actual neuronal network responsible) is inaccessible, such models can only be descriptive, not explanatory. Thus they cannot be verified by reference to any depth of physiological representation they may have, and the similarity that bears to the observed building blocks known to comprise the real system.

#### Receptor- Based Models

The authors of another group of feeding models feel that the type of neural model presented by Hirsch (1978) and Barnwell (1978) can be misleading. They would argue that such models are somewhat premature in their concentration on

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\* Actually the system is conceptually quite straightforward. Its mathematical representation however can be a different matter.

the neuronal analogues of feeding and drinking stimuli, and their interactions. Rather, more certainty could be obtained by starting 'from the outside', and working inwards. Thus, the first task should be to discover the response characteristics of the receptors known to subserve feeding or drinking behaviour. Essentially, one should know what is going into a feeding system before trying to say how the system works. Consequently, this group of authors study the responses of various receptors to stimuli known to influence feeding behaviour. The models they develop reflect this belief. For example, Forbes (1978) studied the interaction between physical (i.e. rumen stretch receptor) and metabolic (energy supply) signals in the ruminant. The contribution of both types of receptor can be implied by direct recording of neuronal firing. Perhaps slightly removed from the study of specific receptors, but in the same vein, lies the work of Booth (1978), who has studied the flow of energy from food in the rat and related this to feeding behaviour.

### Abstract Models

A third group of researchers attempt to analyse the problem from a somewhat more abstract, or non-physiological, angle. Thus Zeeman (1978) has presented a model of anorexia nervosa based upon catastrophe theory. The problems normally tackled by this type of researcher are often by their nature presently intractable to reductionist techniques, yet may be of considerable clinical significance. Obesity is perhaps another example of such a type of problem.

Within this group one could also perhaps include models that place an emphasis upon intangible, 'fuzzy' variables, such as perceived palatability of a food. A classic example of this would be Wirtshafter and Davis (1977). One cannot deny the presence, indeed great significance, of such factors in the control of feeding. Their incorporation in a model is however particularly difficult. Models by their nature demand that all inputs and variables be very specifically defined- this indeed is a source of their strength and rigour in testing hypotheses. However, it is difficult to avoid a considerable degree of ambiguity in attempting to define such intangible concepts as palatability, anticipation, etc.

Each approach has both its strengths and weaknesses, and individual preferences are most likely only to represent one's particular research interest. It is apparent that any complete theory of feeding will have to incorporate aspects of all the above types of model. Steps in this direction have been taken, but one is frequently hampered by the tendency for such studies to rapidly become multi-disciplinary, and lead the unwary researcher into unknown and daunting (if interesting) territory. Perhaps the work of Toates (1978,1981) could be cited as examples of this latter approach. Although undoubtedly more difficult than the purely theoretical or neurophysiological models, the multi-disciplinary model must be the ultimate aim. After all, it is in complex models that computer-based formal representations come into their own, because only then do they begin to exhibit the counter-intuitive emergent

properties so beloved by those espousing the advantages of systems modelling, but so rarely produced. A simple model or hypothesis can be represented by any one of a range of techniques, with no particular advantage accruing to any. Complex models however can only be rigourously tested by formal representation, on a computer. Complex models are most likely to be multi-disciplinary, and thus one may argue that the techniques of systems analysis and computer programming have arrived just in time to uphold in this modern world of diverse sciences the Baconian principle of analysing a corpus of knowledge for the common threads of experience. Tomorrow's renaissance man will need the computer to guide him. It is hoped that the model presented here permits just one very small step to be taken in this direction.

Drinking Models

The analysis of physiological systems with the specific aim of understanding their contributions to behaviour does not have such a long history, nor has it received such attention. This is not surprising; the academic impetus behind the study of physiological systems, and in particular human systems, is largely created by the need to understand clinical and pathological states. Nevertheless, several attempts have been made in the area of feeding and drinking. Some tackle individual subsystems, whereas a few have attempted models with a wider scope. For example, Toates and Oatley (1977) studied the control of water excretion by anti-diuretic hormone. This is of some theoretical interest with regard to, say, the question of why Nature endowed animals with an anti-diuretic hormone, rather than a diuretic hormone. However, Toates and Oatley (1977) is not as deeply based in known aspects of physiology as one would have liked, and as Siebert (1978) pointed out, this can be dangerous. For example, the model lacks any cardiovascular or intracellular fluid regulation. Thus relating ADH release merely to 'blood volume' and arterial pressure is something of an over-simplification, and may only be valid in the short term (a matter of minutes). Similarly, as will be discussed later, the use of 'cellular volume' as a causative (rather than correlational) influence on ADH release is unacceptable in this author's view. ADH release has also been shown to be induced by emotional stimuli, suggesting an autonomic nervous system influence. Thus for

completeness one would like to see this system represented, for which, yet again, cardiovascular representation is necessary.

The first broadly-based model that had the specific aim of studying thirst and the regulation of water intake is due to Oatley (1967). The model developed was more of a 'block diagram' approach than a simulation in the sense referred to here. However, it did show that control-system techniques borrowed from engineering could be of significant value in rationalising thoughts about the drinking controllers.

In the same year, Reeve and Kulhanek (1967) presented a promising analogue simulation of body fluid regulation. This paid a good deal of attention to the mechanisms of release and action of ADH, and drinking control. However, it only had one total body fluid compartment, did not consider the role of aldosterone, and somewhat over-simplified alimentary exchange.

The somewhat tentative suggestions made by Oatley in his 1967 paper were made much more specific and rigorous in a subsequent paper by Toates and Oatley (1970). The digital simulation presented in the 1970 paper has since been the standard work in this area. It is the current author's view however that sufficient data are now available to enable this model to be considerably improved upon. In addition, there is an increasing number of experimental observations that cannot be explained by the Toates and Oatley model. Before pointing out areas in which the model could be improved however, it may be beneficial to study it in some depth.



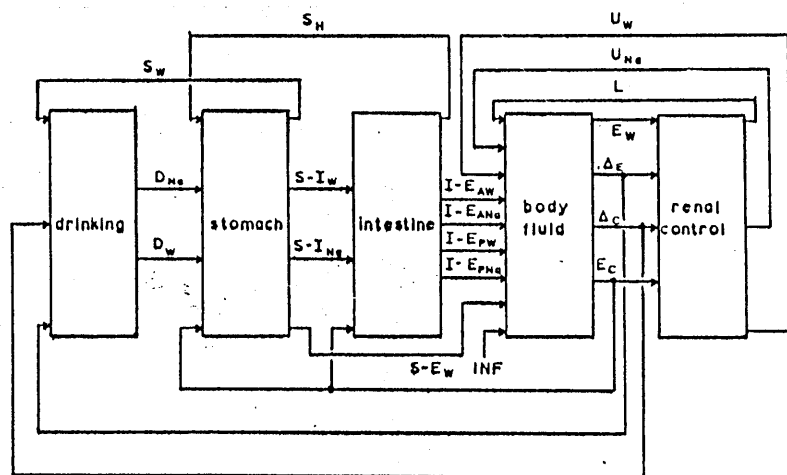


Figure 1.1- Toates and Oatley's (1970) simulation of thirst and water balance.

The relationships between the 5 subsystems that comprise the model are shown in Figure 1.1, along with appropriate notation. This model represents a considerable advance over that of Reeve and Kulhanek (1967) in that it has two body-fluid compartments; intracellular and extracellular. In addition Toates and Oatley's (1970) model, unlike previous simulations by other authors, was developed specifically for the rat, using data on that animal, which particularly in the field of drinking are much more complete than for other species.

The gastro intestinal tract is particularly well represented, there being separate sub-systems for the stomach and intestine. However, the fact that it is only a two compartment system, with no subdivision of extracellular fluid into its interstitial and vascular components, imposes limitations upon the realism the model can hope to attain. Thus, for example, it was necessary to link glomerular filtration rate directly to extracellular fluid volume, an assumption that may be valid in some circumstances, but generally rides roughshod over the large body of research on renal haemodynamics, not to mention the renin-angiotensin system. For similar reasons, autonomic controls are absent, as are all short- and long-term vascular resistance autoregulators, regarded by Sagawa (1973) as "one of the most powerful controls of the circulation". (p.89) As the vascular system is not represented, it is not possible to analyse much of the data on drinking behaviour that has since been published. For example, the effects of venal occlusion on drinking are of some relevance to the nature of

the extracellular, 'volemic' indicator of dehydration. (Fitzsimons, 1964; Fitzsimons and Moor-Gillon, 1980). Similarly, the system's design precludes analysis of drinking induced by systemic injections of angiotensin, a phenomenon commented upon by for example Fitzsimons and Simons (1969).

Indeed, in his Ph.D thesis, it was conceded by Toates (1971) that considering the two extracellular compartments as one could be inadequate, even for the data then available, as was suggested by the simulation of extracellular volume depletion (Toates (1971), p.293).

The model presented by Toates and Oatley (1970) was predominantly created in order to analyse fluid flows within the animal. Thus inorganic ion metabolism is somewhat simplified. For example, although fluid flows occurred as a consequence of trans-cellular concentration gradients, the actual amount of Potassium within the cells was assumed to be constant, and confined to the cellular compartment. However, the control of intracellular Potassium and its excretion by the kidneys are important functions. For example during water deprivation, a relative diuresis of Potassium occurs. (Elkinton and Winkler, 1944; Dicker, 1949). This is related to a shift of fluid from the intracellular to extracellular compartments, thus helping to maintain plasma volume and an adequate tissue perfusion pressure.

The control of Potassium is likely to be of significance in another area not tackled in depth by the model of Toates and Oatley (1970); the control of feeding and energy regulation. The sub-system representing the

gastro-intestinal tract calculates flows of water and sodium only. Food digestion and uptake are not adequately represented. At the very least this precludes the possibility of studying the effects of starvation, and other experimental manipulations in which the intake of food is reduced, such as fluid deprivation. The inevitable variations in cellular mass that occur during experimentally or self-imposed food restriction are very likely to be of considerable relevance when studying the drinking responses of animals following a period of water deprivation. Despite an acknowledgement of the problem by Toates (1978), this aspect has so far been ignored in simulation models of drinking, a most unfortunate omission. It is felt that careful analysis of a more complete model incorporating these controls can help resolve some of the apparent paradoxes currently causing concern in the study of drinking behaviour. For example, Blass and Hall (1976) have paid considerable attention to the phenomenon of 'voluntary dehydration' discovered by Adolph (1943). This they explained in terms of interactions between 'peripheral' (i.e. orogastric) and 'central' stimuli. Whilst there may be some truth in this, it is felt that the explanation is too simplistic due to the inadequate attention being paid to the animal's energy state.

In recent years, hormonal influences on drinking have been given considerable attention. Angiotensin has received the large share of this (see for example Fitzsimons, 1975); slightly more controversial has been the role of ADH (Szcepanowska-Sadowska et al, 1982). ADH and aldosterone are

represented in Toates and Oatley (1970), but yet again the lack of a cardiovascular system prevents one from examining either the hormonal systems, or their contribution to drinking behaviour and fluid regulation in anything but the simplest sense; the 'fine grain' of the model is simply too large for this sort of analysis. The renin-angiotensin system is not represented at all. Thus the possibility (indeed probability) of interactions between hormonal systems cannot be studied. This could be of considerable benefit in making sense of the vast body of research available on ADH, aldosterone and the renin-angiotensin system.

Arguments about the nature of the intracellular and extracellular stimuli to drinking, especially the former, have been raging for some years. Bengt Andersson and his colleagues, (e.g. Andersson, 1953, 1978) studying the goat, have long maintained that the intracellular stimulus to drinking is a Sodium receptor, detecting changes in the cerebro-spinal fluid Sodium concentration. They appear however, to be something of a beleaguered minority. Most workers place greater faith in the suggestion originally made by Gilman (1937), that the critical stimulus for drinking is loss of water from inside the cells. Happily for those who enjoy controversy, there is an adequate supply of conflicting experimental data, so the question is unlikely to be settled in the near future. However, it is considered possible that closer examination of a simulation incorporating cellular water and inorganic ion metabolism may help resolve the dispute. One may at last be able to

begin drawing together the common threads that run through the available data, and determine whether there really need be a conflict after all, or whether it simply resolves itself to species differences. (McKinley, Denton et al, 1980).

It has long been suspected that the extracellular (volemic) receptors involved in drinking reside in the low-pressure, venous side of the cardiovascular system (Fitzsimons, 1964). However, their exact nature and similarity, if any, to ADH receptors also known to lie in this area is unknown. So far, no contributions have been made to this subject by simulation techniques, as no adequate model of rat cardiovascular dynamics exists.

For several reasons, the paper by Blass and Hall (1976) was a significant contribution to the study of drinking. First, it presented its conclusions and theories not as a verbal model, but in the more rigorous form of control diagrams. More importantly however, it revived interest in peripheral controls of drinking. Although the simulation of Toates and Oatley (1970) did point out the need for short-term controls of drinking, a role best fulfilled by oro-gastric stimuli, subsequent attention had been concentrated almost exclusively on central mechanisms.

Earlier theorists, for example Cannon, (1932) placed particular emphasis on peripheral changes, such as a dry mouth or empty stomach as the initiators of motivated behaviour. Their extreme attitudes about the importance of peripheral influences have since been rejected, and rightly so, by their successors. However, this very rejection

resulted in an over-emphasis being placed on central initiators of behaviour. Hundreds of studies have been dedicated to analysing the central neurological and neurochemical substrates of behaviour, whereas very little work has been conducted on the nature of peripheral stimuli. As Blass and Hall (1976) put it, "In our zeal to repudiate the 'peripheralists', we may have thrown out the baby with the bath water". (p.372). A point rarely made, yet one that should be placed on a plaque in the office of every neurophysiologist is that it is not much use studying the logic of the brain if one does not know the nature of the signals being input.

Despite their realisation of the need for peripheral, short-term influences in drinking behaviour, Toates and Oatley (1970) presented only a fairly rudimentary system to subserve drinking behaviour. Drinking initiation is still determined by 'central' factors, reflecting intracellular and extracellular fluid states. Short-term peripheral influences are used only to terminate drinking. Such systems are necessary in order to provide a rapid indication of fluid drunk. Without this, the system would 'oscillate', an exactly analogous situation to that observed in Milhorn and Guyton's (1965) study of Cheyne-Stokes breathing.

The study of these oro-gastric, short-term feedback loops could cast light on several areas which at present appear somewhat confused. It would, for example enable one to examine the individual components of the drinking stimulus, and thus make some sense of the apparent paradox that previously dehydrated rats infused with adequate water

to restore normal balance still drink (e.g. Miller, Sampliner and Woodrow, 1957; Nicolaidis and Rowland, 1975). In addition, one would expect that many of the observed interactions between feeding and drinking may be mediated by combinations of such peripheral stimuli (at least in the first instance) rather than central mechanisms. Some work in this direction has been published by Toates (1978). These interactions are likely to be complex, and may be best interpreted by means of a formal model.

Finally, with an adequate model of both central and peripheral drinking stimuli (and inhibitors) it may even be possible to tackle some problems of theoretical interest in the motivation of behaviour. For example, one may be able to determine whether incentive motivation, the idea that water itself can act as a stimulus to drinking, (e.g. Bindra, 1978), is a more parsimonious explanation of motivated behaviour than conventional approaches. Such a break from the tradition of simple homeostasis-based theories may be controversial, but could help unify the theories of the experimental psychologist and the ethologist. This may parallel the changes in attitude expressed by Herrnstein (1977). Originally an ardent behaviourist, he has now adopted a somewhat more 'ethological' stance. In addition, rather than holding the traditional behaviourist view that a reinforcing stimulus must act to restore a homeostatic equilibrium, he now believes that the motor activity normally involved in ingesting the desired substance is in itself reinforcing. This does not necessarily challenge the basic concepts of homeostasis; however, it may well be the



type of approach necessary to expand the concept beyond the current, somewhat simplistic, analysis.

Requirements of an Adequate Model

Although the two-compartment model as presented by Toates and Oatley (1970) has been of tremendous use in understanding some drinking phenomena, experimental knowledge has now advanced to the point where its strength lies in highlighting the situations where it fails. As such of course, it acts as an indispensable basis for future simulations. This is not to decry their work; it is merely one step in the series of successive approximations to truth, of which it is hoped the model presented here will be another. In time, this too will be superseded.

Thus to conclude, it is felt that a more up to date model of rat drinking behaviour should embody the following features;

a) It should be a 3-compartment system, consisting of intracellular, interstitial and vascular compartments.

b) It should include a reasonably complete description of rat cardiovascular dynamics.

c) It should have an adequate description of relevant hormonal systems, such as ADH, the renin-angiotensin system and aldosterone.

d) It should have sufficiently realistic renal dynamics to allow a sensible representation of the systems in c)

e) It should incorporate the autonomic nervous system, including its effects on the cardiovascular and hormonal systems mentioned above.

f) It should have as complete a description of known peripheral influences on drinking behaviour as is possible.

g) It should be able to represent the 'central', i.e. intracellular and extracellular stimuli in physiological terms, such as one would expect to see in a physiological simulation. For example, such gross simplifications as 'cell volume' and 'blood volume' will not do.

h) It should have adequate representations of intracellular Sodium and Potassium metabolism, to enable realisation of g)

i) It should have a reasonably complete description of energy balances within the animal, in order to represent realistically the effects of starvation, etc.

j) The gastro-intestinal tract must be able to represent turnover of food, as well as water and inorganic ions.

CHAPTER 2A Microcomputer-Based Simulation of Rat Body Fluid DynamicsIntroduction

The simulation presented in this section, generally referred to as the 'small rat', was designed for a specific purpose. For some years, lecturers on the Open University Summer School course (SD286), had experienced some difficulty in conveying to their students the nature of the relationships between body fluid compartments, and how the various stimuli contributed towards the motivation of drinking behaviour. Eventually, it was realised that the most effective way would be to create a computer simulation of rat body fluid dynamics. Whilst using this simulation, the student would be presented with a variety of situations in which the simulated rat had received a physiological intervention of some sort. The student would then have to suggest a further, remedial intervention. Points were awarded according to the effectiveness (or otherwise!) of this remedial intervention, and the final score indicated the extent of the student's understanding. Some examples of the type of situation presented to the rat are infusions of hypertonic saline, haemorrhage, and diabetes insipidus. In each case the student had to either estimate the salinity (if any) of drinking water offered in order to repair the deficit, or, in the case of diabetes insipidus, estimate how much water would be drunk in a given period.

The requirements of an educational model such as this

impose certain constraints on the model's designer. Essentially, these all come down to the need for speed, without unduly impairing accuracy. Thus for example, it is necessary for the model to run 'on-line', i.e. it must come up with the necessary predictions immediately. Despite the fact that this simulation was to be run on a large 'main-frame' machine (DEC 20), it was still necessary to design a compact system, yet one that retained a greater degree of realism than is currently available in any other model. If the model were too large, then the computer may not be able to respond quickly enough to the student's suggestions. None of the models previously published by Toates (e.g. 1971) was adequate, because it had to be able to realistically represent the drinking responses to haemorrhage. The lack of a cardiovascular system would have precluded this. Thus a 'three compartment' model, consisting of intracellular, interstitial and cardiovascular components, had to be created.

A related problem is that of the 'iteration interval'. Digital computers, by the nature of their design, generally execute the commands that constitute a program in a sequential order, starting at the beginning, and proceeding one at a time until they reach the end, at which point they can either stop or be returned to the beginning, to repeat the process. The latter is generally the case in a simulation of this nature. Thus when a program representing a control system is run, the computer in effect runs through the program many times, updating its estimates of variable values on each occasion. Each time the computer cycles

through the entire program, updating itself, is termed an 'iteration'. The amount of 'rat real time' represented by each iteration can vary. In this particular simulation, each iteration represents two minutes of real time. Thus thirty iterations represent one hour, and so on. The more calculations a computer has to do, the longer it takes to come up with the answer. Consequently the iteration interval is an important determinant of computer response times; the longer an iteration interval, the better. However, this can produce problems of its own, most notably that of instability. Therefore the aim is to find an iteration interval that meets the demands of realism, yet prevents instability and permits a rapid response from the computer. As mentioned above, the iteration interval of this simulation is generally two minutes, but it can be varied, to suit the phenomenon being studied.

The simulation was written and developed in 'BASIC' on a micro-computer (Commodore 64). Since this was several orders of magnitude slower than anything it would ever run on for a student, it was felt that 'if it'll run on this it'll run on anything'. In the event, it was found that a very realistic model could run on this type of system, and it is quite feasible that further development would enable it to run well enough to justify its use as an educational model on just such a micro-computer. Basically, this would involve converting it to integer-based arithmetic and 'compiling' the converted model. If necessary, one could link two micro-computers (via RS232 serial ports); one would cope with the simulation, and the other with the graphics.

Given the low price of small home-computer systems, even this last combination could be created for less than a thousand pounds. Some of the more recent, faster machines (such as the B.B.C. micro) would find the task even easier.

Having been developed on a micro-computer, the 'small rat' simulation was re-written in 'PASCAL', and now forms the central module of an Open University educational simulation.

Because of its relative simplicity, the 'small rat' simulation is described and discussed before going on to look at the larger version. This, it is hoped, will enable the reader to grasp the fundamental problems without being overwhelmed by a mass of detail. However, it should be pointed out that development of the larger simulation commenced several years before the much more rapid development of the simulation presented in this chapter. In addition, the smaller simulation is, as far as one can be aware, fully operational; on the other hand, it is felt that the 'large rat' is still in need of some 'fine tuning'. Until such time as certain aspects of its design can be elucidated, its scope of validity must be regarded as somewhat narrower than that of the smaller simulation. Already however, within this range, it has enabled a much greater depth of analysis. This is evidenced by the study of fluid dynamics following gastric and cardiovascular infusions. The new theory of intracellular-induced drinking, described in Chapter 15, has been converted to a working system and is now incorporated into the 'large rat'. This latter simulation will act as a much more appropriate

general medium for the analysis of this individual component, as it is probably too large for the 'small rat'. In addition, it is anticipated that future work will concentrate on this larger model, as it undoubtedly has the greatest potential.

As discussed earlier, the simpler simulation is presented first. Nevertheless, the rationale behind the system's design has to be explained and justified; it is not always permissible to postpone such detail until later. Consequently some fine detail is regrettably necessary, but wherever possible in-depth discussions are presented later.

### Brief Description

The simulation to be described here is a three compartment model, i.e. it calculates fluid contents and flows across the boundaries of the cardiovascular, interstitial fluid and intracellular compartments. Homeostasis of Sodium and Potassium ions is also maintained. Intake of food and water is governed by systems within the program that detect energy deficits and dehydration respectively.

Renal output of water and ions is determined by a combination of hydrostatic and hormonal factors; insensible water loss is determined by ambient temperature and day phase.

This simulation is essentially a simpler version of the 'large' simulation, described later. However, it should be stressed that the term 'simpler' is used with respect to the more complete simulation only. With the exception of this



latter system, it is still the most complete description of rat body fluid dynamics available. In the following sections, the structure and function of each subsystem in the program is described in greater detail. Some simulations are then presented and examined.

Cardiovascular System

The cardiovascular system is bounded on one side by the gastro-intestinal tract, and the interstitial fluid compartment on the other. Thus its role in overall body regulation is crucial; it acts as the essential medium through which nutrients reach the cells, and waste products transported away. In order to achieve this, an adequate pressure in the arteries needs to be maintained, to perfuse the tissues via the capillaries. There are a large number of regulatory systems, both short and long-term, that serve to maintain this adequate pressure. It is this multiplicity of regulatory mechanisms that makes the cardiovascular system appear so complex. In all cases however, the ultimate aim is this single factor of ensuring an adequate flow of blood past the body tissues, without which they will rapidly degenerate and die. Of all tissues, the brain is probably most susceptible to damage in this way.

Flows of water and electrolytes into the vascular compartment from the gastro-intestinal are determined by osmotic pressure gradients and active transport (see elsewhere). Fluid flows from the cardiovascular compartment into the interstitial compartment are induced by net pressure differences across the capillary walls. Ion flows, however, are determined by concentration gradients; there is no active transport across this boundary.

The cardiovascular compartment is probably the most complex system in this simulation. A reasonably accurate representation of reality is, it is considered, necessary,

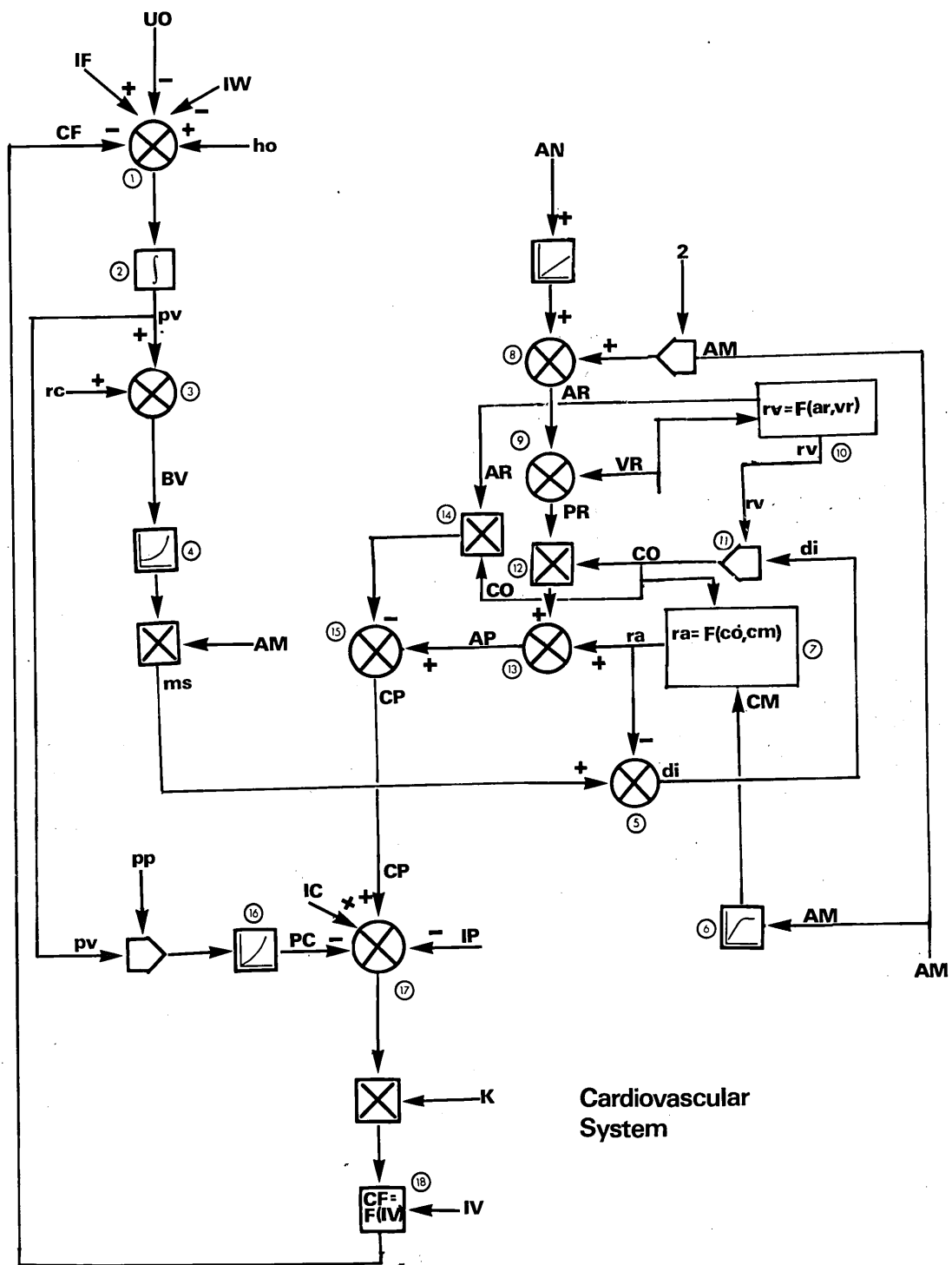


FIGURE 2.1

as it is largely responsible for determining such essential variables as trans-capillary flow, glomerular filtration rate and autonomic nervous system activity. As such this is not an easy system to describe, and it is suggested that the reader refer whenever necessary to Figure 2.1.

The design of this section owes a great deal to the work of Guyton and his colleagues (Guyton and Coleman, 1967; Guyton, Coleman and Granger, 1972). However, these systems were both designed to investigate human cardiovascular dynamics. Consequently many of the functions employed have been altered, to suit the individual needs of the current topic. In order to avoid repetition, full details of physiological data sources are presented in the appropriate section of the 'large rat' simulation. Complete descriptions of all variables used are presented in Appendix I.

Gains or losses of fluid from the cardiovascular compartment can occur by a variety of means. Thus block 1 forms the first vital stage in the calculation of cardiovascular fluid (i.e. blood) volume, by determining the net rate of gain or loss per iteration of the program (see earlier in this chapter for a discussion of iteration intervals). Losses can arise from urinary output or insensible water loss. Conversely, the flow of lymph fluid always acts as an addition to plasma volume, whereas capillary flow and water flow from the gut can be either positive or negative. Block 2 integrates the successive estimates of net flow to give plasma volume; block 3 then

adds the volume occupied by red blood cells to give total blood volume. With the exception of the incorporation of insensible water loss in block 1, the system in blocks 1 to 3 are identical to those used by Guyton (for references, see above) and his colleagues. Estimates of normal plasma and red blood cell volumes are from experimental rat studies. Those interested may wish to refer to the appropriate section of the 'large rat' simulation, where the topic is discussed in greater depth.

Block 4 calculates mean systemic pressure, which may be regarded as a measure of the degree of filling of the vascular system. The greater the degree of filling, the greater is mean systemic pressure. In this respect, the vascular system can be likened to a water filled balloon; as more water is added, the higher the pressure inside the balloon. However, in this case the ability of the balloon to stretch can be varied, according to the activity of the autonomic nervous system. Thus an increase in autonomic activity has the effect of increasing mean systemic pressure for any given volume of fluid contents. This technique again is identical to that used by Guyton and Coleman (1967). However the relationship between blood volume and mean systemic pressure has necessarily been altered, to employ values of blood volume appropriate for the rat, rather than the human. The gradient is as before.

Block 5 subtracts right atrial from mean systemic pressures to give the mean arterio-venous pressure gradient. Guyton (1955- dogs) demonstrated that flow of blood into the heart is linearly related to mean systemic

pressure minus right atrial pressure. For want of more detailed information, it is assumed that the same situation will apply in the rat.

Block 6 is responsible for determining the effect of autonomic activity on the heart. Under normal circumstances, the pumping ability of the heart is directly related to the degree of autonomic excitement it receives. However, when arterial pressure is above about 150 mmHg, the heart's ability to pump against the back pressure in the aorta begins to fade, and can actually reach zero if pressure is high enough (Guyton and Coleman, 1967).

Block 7 calculates right atrial pressure. Essentially, this uses a 'Starling curve of the heart' (Patterson and Starling, 1914- dogs). As cardiac output rises, the 'back pressure' of blood in the right atrium also rises. This can however be varied by autonomic activity. Autonomic excitation of the heart will increase its pumping activity, and thus tend to reduce right atrial pressure below the normal value for any given cardiac output. The function used is derived empirically, but is designed to emulate the data of Patterson and Starling (1914), and Guyton and Coleman (1967). The effect of autonomic activity is represented by using it as a 'divider'. This in effect shifts the curve described above in the appropriate direction whenever autonomic activity departs from its normal value of one. Again, no rat data are available, but there is no reason to suspect that in this respect the rat would behave in any different way than a dog, or human.

Block 8 determines the resistance of the arterial

system to blood flow. The arteries themselves offer negligible resistance to the flow of blood; most occurs in the capillaries and pre-capillary arterioles. The resistance of these arterioles can be varied in accordance with the state of the vascular system. A shortage of blood promotes constriction of the arterioles, which serves to maintain arterial pressure. This in turn provides an adequate head of pressure to perfuse essential body tissues. This system forms an important short-term regulator of arterial pressure. In this simulation, two factors serve to control arterial resistance; plasma angiotensin concentrations and autonomic activity. In this respect the model presented here differs from Guyton and Coleman (1967), which only uses autonomic activity, angiotensin not being represented. Angiotensin is the most powerful vasoconstrictor substance known (Guyton, 1976, p.262), and is released in response to a decrease in arterial pressure. Both angiotensin and autonomic activity can stimulate constriction of the peripheral arterioles, increasing resistance to blood flow. Thus the two main short-term determinants of arterial resistance are autonomic activity and plasma angiotensin concentration. In this simulation each influence is given an approximately equal effect. Unfortunately, no evidence is available to demonstrate their relative influences, either under normal or abnormal circumstances. The effects of both autonomic activity and angiotensin on arterial resistance are expressed as a multiplier, applied to a basal level of arterial resistance. The basal level was determined empirically by reference to

normal values of arterial pressure and cardiac output in the rat (see 'large rat' discussion for references). The gradients pertaining to the relationships between autonomic activity, angiotensin and the arterial resistance multiplier are, again, largely arbitrary. About the best that can be said of them is that they are definitely in the right direction. They do however appear to work very well, and have thus survived this test of validity. Block 9 sums arterial and venous resistances to give the total peripheral resistance to blood flow. As in Guyton and Coleman (1967), it has been assumed that venous resistance (not controlled in this simulation) comprises only about 15 per cent of total resistance. This figure was derived from dog experiments, but may reasonably be transferred to rats.

Block 10 calculates the resistance to venous return, using an expression determined experimentally by Guyton et al (1959- dogs), and adapted for use in this simulation. In the experiment, resistance to venous return was determined while venous resistance was altered by constriction of major veins, and arterial resistance was altered by injection of microspheres into the arterial circulation. Although the relative contributions of arterial and venous resistances to resistance to venous return have been retained, the constant has been increased from 32 to 40; a value derived empirically, considering published aspects of rat cardiovascular dynamics.

Block 11 divides the pressure gradient for venous return (derived in block 5) by resistance to venous return to give venous return of blood to the heart. Except for



short transient periods of around a few seconds, venous return is equal to cardiac output. This approach is as used by Guyton and Coleman (1967).

Blocks 12 and 13 derive arterial pressure. First, by analogy with Ohm's law, block 12 calculates the pressure gradient between the arteries and the right atrium by multiplying total peripheral resistance and cardiac output. This pressure gradient approximates to arterial pressure. To actually deduce arterial pressure, however, it is necessary to add right atrial pressure. This is accomplished by block 13. Again, this technique is derived from Guyton and Coleman, (1967).

Blocks 14 and 15 calculate capillary pressure. Block 14 calculates the pressure gradient in the arteries by multiplying cardiac output and arterial resistance. Block 15 then calculates capillary pressure, by subtracting the pressure gradient in the arteries from arterial pressure. Capillary pressure is a major determinant of fluid flow across the boundary between the vascular and interstitial compartments. It participates in 'Starling's capillary equilibrium' (Starling, 1896), discussed later.

The osmotic pressure of plasma proteins is directly determined by their concentration, and this is calculated by block 16. The power function used is derived from the experimental studies of Ott (1956). The experiments were conducted on dogs, but there is no reason to doubt their validity to rats. The fit of this function to the experimental data is very good, and applies within a wide range of concentrations. The osmotic pressure normally

exerted by plasma proteins is about 20 mmHg (for references, see the appropriate section in the 'large rat' discussion).

The actual flow of fluid across the vascular/interstitial boundary is determined by a range of hydrostatic and osmotic forces, which combine to give a net ultrafiltration pressure. This is calculated by block 17, and is a representation of Starling's law of the capillaries. The actual rate of fluid flow across the capillary walls is normally directly proportional to this net ultrafiltration pressure. The 'ultrafiltration coefficient', which describes the permeability of the vascular/interstitial boundary to fluid, has been investigated in rats (see 'large rat' discussion). Thus the value used here has been experimentally validated. Under some circumstances involving dehydration however, flow from the interstitial fluid compartment to the vascular compartment is restricted. The factors involved in this, briefly shown in block 18, are dealt with in greater detail in the description of the interstitial fluid system. The effect of this is to reduce the ultrafiltration coefficient, previously alluded to.

Interstitial Fluid Compartment

The interstitial fluid lies, as its name suggests, in the spaces between the cells. Substances transported to the capillaries by the vascular system still have to reach the cells, where they can be utilised. To achieve this, substances need to cross the vascular/interstitial boundary into the interstitial compartment, from which they can gain access to the cellular boundary.

However, only a small proportion of the interstitial 'fluid' actually occurs as freely flowing fluid. Under normal circumstances, the greater proportion occurs as a gel (Guyton, 1976, p.402). This gel permits the relatively free diffusion of diffused substances, yet restricts water movement to a minimum.

The free fluid contained within the interstitial spaces is more generally referred to as lymph fluid. The importance of this fluid in physiological regulation has been examined by Mayerson (1963). The presence of a high pressure vascular system, designed to ensure adequate tissue perfusion, has resulted in a constant slight filtration of plasma across the capillary walls and into the interstitial spaces. Thus phylogenetically, a need arose for a system capable of draining this excess fluid from the interstitial compartment, back into the vascular system. In this sense, the lymph system can be regarded as a homeostatic mechanism, serving to prevent the build-up of an excessive fluid volume in the interstitial spaces. Thus it is perhaps not surprising to find that the rate of lymph flow is

directly proportional to the pressure of fluid in the interstitial spaces (Guyton and Coleman, 1967), nor that blockage of any of the lymph ducts can result in oedema of the area normally served by that duct.

As a consequence of its intermediary position, flow of fluid into the interstitial compartment can arise from two sources. First, fluid can flow across the capillary walls, from the vascular compartment, as a consequence of the net ultrafiltration pressure (Starling's capillary equilibrium-see the cardiovascular section). Second, fluid can cross the boundary between the cellular and interstitial compartments as a consequence of osmotic pressure gradients. In either case the flows can be into or out of the interstitial compartment. Fluid is returned to the vascular compartment via the lymph system, which acts as part of an interstitial volume-regulating mechanism. These mechanisms apply only to the small fraction of interstitial water that occurs as free fluid. The majority is held as a gel, through which substances are transported by diffusion. Nevertheless, there is evidence that the free fluid that is held in the interstitial compartment can act as a 'reserve', helping to maintain plasma volume in times of fluid deprivation (Koven, Gallie et al, 1972; Taylor, Gibson, Granger and Guyton, 1973).

Thus this system acts as an intermediary between the vascular and intracellular compartments. Fluid cannot reach one from the other without first entering this compartment. A control diagram, describing the system's design, is shown in Figure 2.2. A similar system has been used by Guyton and

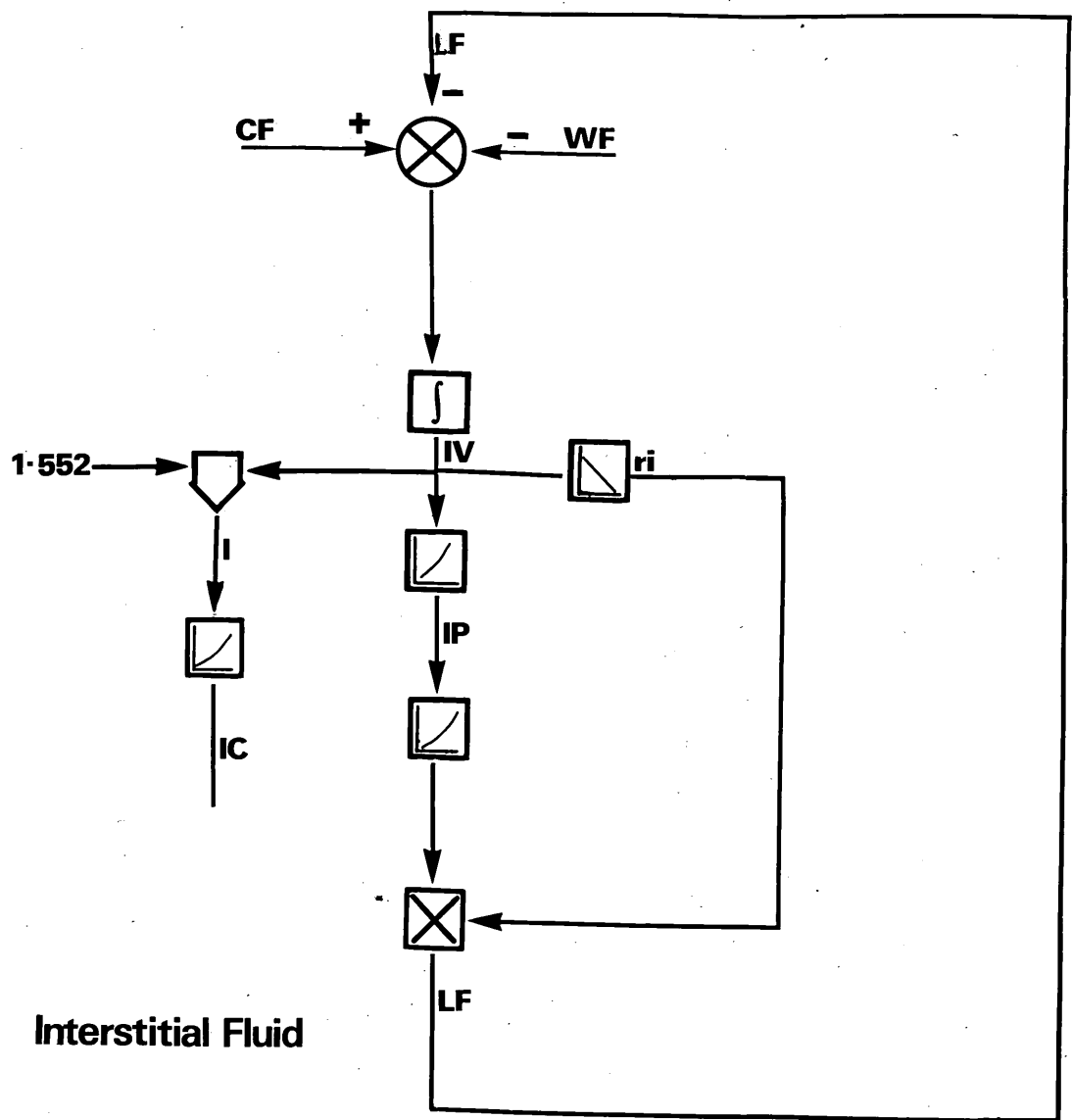


FIGURE 2.2

Coleman (1967). Note that neither Figures 2.1 nor 2.2 show the turnover of Sodium or Potassium ions. As far as these ions are concerned, the vascular and interstitial compartments are treated as one. Thus their metabolism is described elsewhere, as they have no direct bearing on the current topic, i.e. determinants of fluid flow between vascular and interstitial compartments.

The net change in interstitial fluid volume in any one iteration of the program is given by summing trans-capillary flow (cf), fluid gain or loss from the cells (wf), and lymph flow (lf). Integrating this over a series of iterations gives the interstitial fluid volume (iv). This volume, as do most variables achieved by integration, have an initial value allocated, derived from published data. These are discussed in greater depth in the 'large rat' simulation, and are shown in the appropriate listings (Appendix II).

In describing the volume-pressure characteristics of the vascular compartment, it was likened to a fluid-filled elastic balloon. A similar relationship is found in the interstitial fluid compartment, except this time one does not have the complication of variable compliance due to the autonomic nervous system's activities.

Trippodo (1982) showed that rats, as most mammals, have a negative interstitial fluid pressure. The normal value is about -1.2 mmHg. This has also been indirectly corroborated by estimates of the other factors underlying capillary equilibrium. In fact the majority of this tendency to a negative interstitial pressure is due to the imbalance of forces at the capillary membrane. The functional

significance of creating a partial vacuum in the interstitial spaces is that it causes all the contents to be compacted, thus acting as connective tissue. Consequently to a large extent, one can consider that below a certain volume, the interstitial compartment is effectively 'dried out' of free fluid. The relationship between interstitial fluid volume (iv) and interstitial pressure (ip) is based upon dog work by Guyton (1965), and adapted for use in this simulation, in order to accommodate the completely different range of interstitial fluid volumes. As interstitial fluid volume decreases, it becomes progressively more and more difficult to extract fluid from the interstitial compartment; there is less free fluid available. This has the effect of reducing outflow of fluid into another compartment; on the other hand, flow into the interstitial compartment from another is unimpeded. This tendency is incorporated in block 4 of Figure 2.2, and is used to help determine all fluid losses from the interstitial compartment, whether they be due to hydrostatic or osmotic pressure gradients. There is unfortunately a lack of information on this topic, and therefore the relationship used is somewhat arbitrary. It was determined using reasonable physiological limits of interstitial volume.

The capillary walls contain many 'slit pores', through which fluid and inorganic ions can freely pass. However, they pose a considerable obstacle to larger molecules, such as plasma proteins (Guyton, 1976, p.386). Thus the concentration of proteins held in the interstitial compartment is not as high as in the vascular compartment,

but they still exert a significant osmotic effect, and help to maintain equilibrium between the vascular and interstitial compartments. This interstitial colloid osmotic pressure (ic) is calculated by the final block in Figure 2.2. The concentration/ pressure relationship used is the same as that in the vascular compartment. Normal values are around 5 mmHg (Guyton, 1976, p.394).



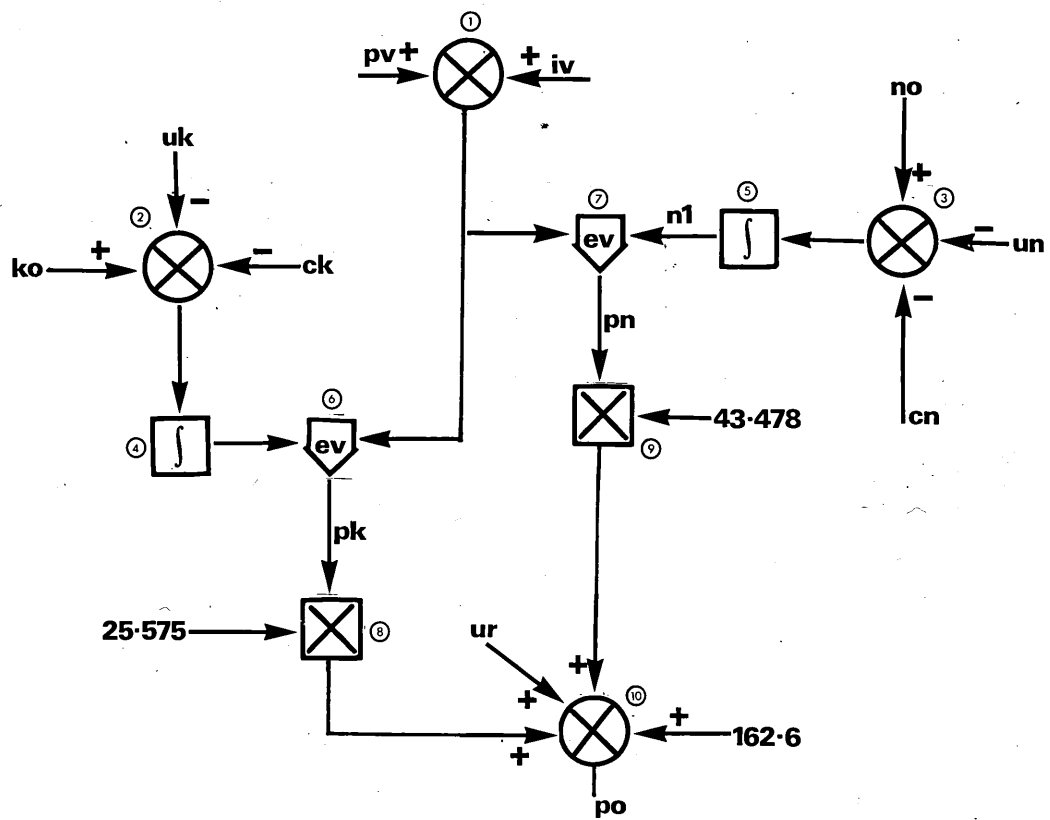
Plasma/ Interstitial Sodium and Potassium Metabolism

As mentioned earlier, the vascular and interstitial compartments are treated as one when considering the turnover of inorganic ions. This incurs only a minor sacrifice in accuracy of representation, but permits considerable savings in program size. Generally, the concentrations of the principle electrolytes with which the current simulation is concerned (Sodium and Potassium) have the same concentrations in both vascular and interstitial compartments (Guyton, 1976, p.432). In addition, equilibrium between the two compartments following a disturbance in osmolality can be restored within a few minutes (e.g. Hevesy and Jacobsen, 1940- rabbit). Thus it is felt that in this case one can be justified in subsuming vascular and interstitial electrolyte dynamics under one category. In the large rat, which does not have constraints of program size imposed upon it, this assumption is not made. There, the electrolyte dynamics of vascular and interstitial fluid compartments are treated separately.

The system used in this simulation to represent extracellular ion metabolism is shown in Figure 2.3.

The volume of distribution of inorganic ions in this compartment is plasma volume (pv) plus interstitial fluid volume (iv). This is derived in block 1, Figure 2.3, and referred to as 'ev', extracellular volume.

The basic systems simulating Potassium and Sodium ion metabolism are very similar. Thus except where stated otherwise, this one description may be taken to stand for



Plasma & Interstitial Fluid  $\text{Na}^+$  &  $\text{K}^+$

FIGURE 2.3

both ions.

Flow of ions to or from the extracellular compartment can arise from a variety of sources. Ions ingested with food or drinking water are released from the gut into this compartment. On occasions however, ion flow can occur down a concentration gradient into the gut, reversing the normal direction of flow. The gastro-intestinal flow of Sodium is represented by the variable 'no'; the corresponding Potassium flow is 'ko'.

Urinary flows of Sodium and Potassium are always in one direction; they always represent losses from the extracellular ion 'pool'. Urinary Sodium and Potassium losses are represented by 'un' and 'uk' respectively. Flows from the intracellular compartment on the other hand, can be either positive or negative. Under equilibrium conditions, the net flows between the two compartments will tend towards zero. The cellular loss or gain of Sodium and Potassium are represented by 'cn' and 'ck' respectively.

Blocks 2 and 3 represent summing points for all losses or gains of Sodium and Potassium, thereby deducing the net flow rates. Blocks 4 and 5 then integrate these net flows, to give the total size of the ion pools at any one time. Blocks 6 and 7 divide these figures by the volume of distribution, i.e. 'ev', to give the extracellular electrolyte concentrations ('pk' and 'pn'). Normal Sodium concentration is around 3 mg/ml, and Potassium concentration is about .159 mg/ml. Blocks 8 and 9 convert extracellular Potassium and Sodium concentrations respectively, from mg/ml to mOsmoles/l. The constants in each case represent

1000/electrolyte atomic weight.

The final block in this section (10) sums all contributions to plasma osmolality, producing the variable 'po'. This is used elsewhere in the simulation to calculate concentration gradients across compartment boundaries. The normal value is around 299 mOsmoles/l. The variable 'ur' enables one to simulate the effects of urea infusion. The figure of 162.6 shown in Figure 2.3 (block 10) illustrates the effects on total plasma osmolality of factors other than Sodium and Potassium, and which are not controlled in this simulation. This consists of Chloride (114.9 mOsmoles/l), Calcium (2.5), Magnesium (1.5), bicarbonate (27), phosphates and sulphates (2.5), amino acids and lactate (3.4), glucose (5.6), protein (1.2) and urea (4 mOsmoles/l). Values are for human data (Guyton, 1976, p.432), but reasonable applicability is assumed.

Intracellular Compartment and Energy Metabolism

About 60 per cent of the fluid in the average human is contained inside the millions of cells comprising the body (Guyton, 1976, p.425). Put another way, this means that 40 per cent of total body weight consists of intracellular water (Rolls and Rolls, 1982, p.11). Collectively, this aggregate of individual cell contents is termed the intracellular compartment.

Unlike the interstitial and vascular compartments, the intracellular fluid contains only small quantities of Sodium and Chloride ions. However, it contains large quantities of Potassium and Phosphate ions. In addition, the cells contain large quantities of protein, approximately four times as much as the plasma (Guyton 1976, p.432).

Equilibrium between the intracellular and interstitial compartments is maintained by osmosis. This process is of considerable importance to the model presented here, and may be defined as 'a spontaneous net movement of solvent molecules from a stronger to a weaker solution through a membrane which is permeable only to the solvent' (Robinson, 1960). The transfer of water through the membrane of an individual cell in response to an osmotic pressure gradient occurs so rapidly that osmotic equilibrium is restored within a matter of seconds. However, this is not to say that complete equilibrium between the interstitial and intracellular compartments is achieved in a similar time. Fluid usually enters the body through the gut, and then needs to be transported by the blood to all tissues before a

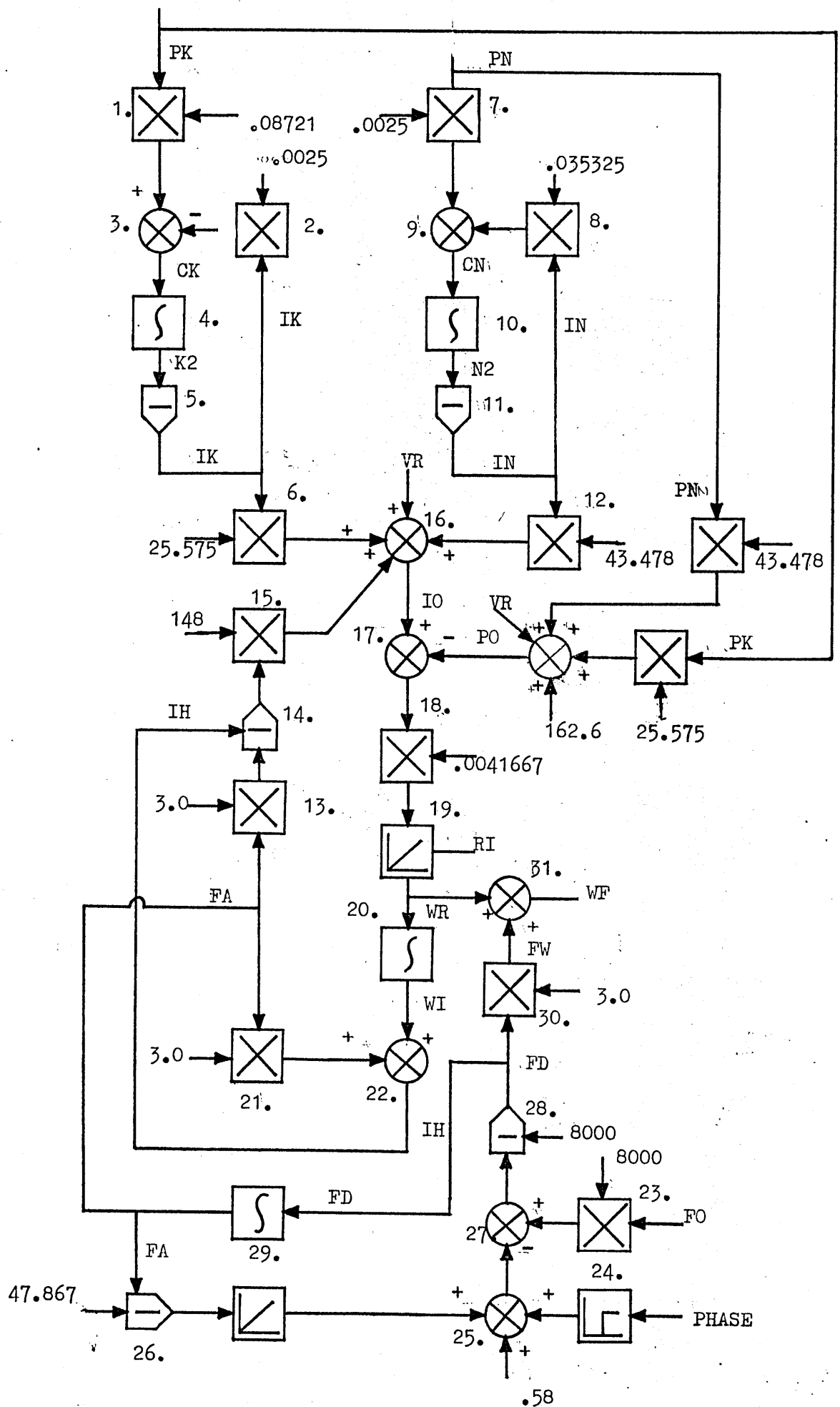


FIGURE 2.4- INTRACELLULAR COMPARTMENT.

new equilibrium can be reached. In the human, this process can take upwards of half an hour (Guyton, 1976).

Like the vascular compartment, the intracellular compartment is fairly complex. Therefore the description given will generally be block by block. A complete control diagram of this compartment is given in Figure 2.4.

The general principles of the system are that osmotic pressure gradients are kept at a minimum, although equilibrium inorganic ion concentrations within the compartment differ greatly from those outside. Water flows across the boundary whenever an osmotic pressure gradient occurs. The intracellular 'dry mass' varies according to the nutritional state of the animal; changes in this dry mass also promote water flow across the boundary.

Block 1 calculates the transport rate of Potassium from the interstitial into the intracellular compartment. This is assumed to be directly proportional to plasma Potassium concentration ( $p_k$ ). The constant used was derived empirically, using known estimates of plasma Potassium concentration, and the assumption that equilibrium between the two compartments following a disturbance would be restored within about 20 minutes.

Block 2 calculates the counteracting flow of Potassium out of the intracellular compartment. Again, it is assumed that flow is directly proportional to the relevant concentration ( $i_k$ ). The constant was derived empirically, using equilibrium concentrations of intracellular Potassium. The constant in block 1 is greater than that in block 2. This is because Potassium is actively transported into the

intracellular compartment, effectively increasing the boundary's permeability in that direction. The net result of this is that the intracellular concentration of Potassium will be much higher than the extracellular concentration. Block 3 sums these two effects to give net change, and block 4 integrates this net change, to give total intracellular Potassium. Block 5 deduces intracellular concentration of Potassium, and block 6 calculates the contribution of this concentration to overall intracellular osmolality, in mOsmoles/l. The constant used in block 6 is equal to 1000 divided by the atomic weight of Potassium.

Blocks 7 to 12 treat intracellular Sodium in an identical way. Note however that the constants in blocks 7 and 8 differ from those in blocks 1 and 2. This is because Sodium, unlike Potassium, is actively excluded from the cells. Thus intracellular Sodium concentration will be lower than that found in the extracellular compartment.

Normal intracellular concentrations for Potassium and Sodium are around 5.54 and .211 mg/ml respectively (Guyton, 1976, p.432).

Blocks 13 to 15 calculate the magnitude of 'other' influences on intracellular osmolality. As can be seen from block 15, the normal influence is 148 mOsmoles/l (Guyton 1976, p.432); however, blocks 13 and 14 vary this according to the relative hydrational state of the intracellular compartment. Normal hydrational state is given by cellular dry mass times three (see later) (block 13); the variable *ih* however also incorporates any additional fluid present. Thus the ratio of these two is the figure by which 148 needs to



be multiplied in order to give the actual 'other factors' effect on intracellular osmolality. Block 16 merely sums all influences to give total intracellular osmolality. Note the presence of variable 'ur'; this, also present in the extracellular compartment, allows the simulation of urea infusion.

Block 17 subtracts extracellular from intracellular osmolality to give the net osmotic pressure gradient across the boundary. Water will normally flow across this boundary in such a direction as to reduce the gradient. As mentioned earlier however, flow out of the interstitial compartment to any other is restricted when the interstitial compartment is relatively dehydrated. Thus when appropriate, the constant determining water flow is reduced. The constant used is derived from data provided by Hevesy and Jacobsen (1940).

Block 20 integrates successive estimates of osmotically induced water flow to give the total fluid so far transferred due to this effect. This is not yet the same as intracellular fluid volume, however. To obtain this, blocks 21 and 22 calculate the amount of water that would normally be present in the intracellular compartment, and adds it to the total osmotically shifted water.

Blocks 23 to 31 are responsible for assessing energy balance, and calculating any consequent movements of water.

Block 23 deduces the rate of energy provision from the gut, in Joules/second (i.e. Watts). The constant value in Block 23 was derived by comparison of approximately normal food digestion rates and metabolic rates in an average rat (LeMagen, 1981).

Blocks 24 to 27 derive metabolic rate, i.e. rate of energy use. LeMagnen (1981) has shown that the metabolic rate is normally slightly higher at night than during the day (the rat is a nocturnal animal). Thus when the day phase indicates night, block 24 increments the lower daytime metabolic rate shown in block 25. Block 26 constitutes a largely hypothetical relationship between the extent of body energy reserves and metabolic rate. Thus when energy stores are depleted, for example during starvation, the animal adapts by slightly reducing its energy requirement.

Block 27 compares the rates of energy yield from the gut and energy usage to give net energy gain or loss for that particular iteration. This net rate is then divided by 8000 (block 28), to convert the net energy flow to net loss or gain of body energy reserve tissue, which for want of a better name will be termed 'fat'. It does of course also include glycogen and protein energy stores. The figure of 8000 is derived empirically, by assessing the weight loss of a food deprived animal, and the metabolic requirements of that animal over the period of food deprivation. The resulting variable, indicating rate of fat deposition, is termed 'fd'.

Block 29 integrates successive estimates of fat deposition rates to give the total fat stores at that particular time.

The aim of block 30 is to calculate the water flows associated with the deposition or destruction of body energy stores. It was estimated that on average each gram of 'fat' would be associated with three grams of intracellular water

(Bintz and Mackin, 1980). Thus the deposition of energy stores results in the enlargement of the intracellular compartment at the expense of the other two. Conversely, starvation results in a release of water from the intracellular compartment. This loss or gain of fluid will result in an osmotic pressure gradient, and thus ions will flow accordingly. Consequently starvation also results in the release of Potassium and to a smaller extent Sodium into the extracellular spaces. It should be pointed out that this system is a gross simplification. An assumption made here is that all water associated with the deposition of an energy store, be it chemically or more loosely bound, forms part of the volume of distribution for intracellular electrolytes. In all probability this is not the case; planned future work involves investigating the nature of intracellular water, and the functions that can be performed by individual components thereof. For the time being however, this system appears adequate; to an extent, the simplicity is a reflection of the main aim of the simulation, which is short-term water homeostasis in a variety of experimental conditions.

Block 31 sums the two causes of intracellular fluid loss (osmotic and energy state) to give total loss/ gain rate. This is largely for the benefit of the interstitial fluid compartment.

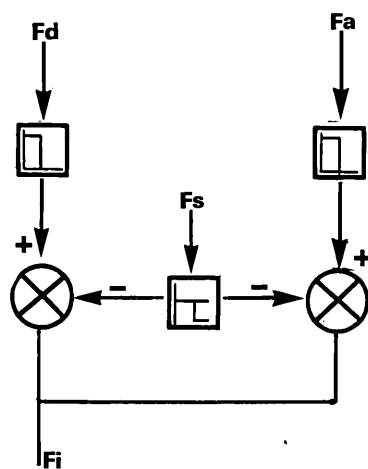
Regulation of Drinking and FeedingDrinking

The regulation of drinking in this simulation is basically as would be predicted by the 'double depletion' hypothesis of drinking that has been popular for a decade or so (e.g. Rolls and Rolls, 1983). (See Figure 2.5(a)). Stimuli from the extracellular and intracellular components of the model summate to give a total drinking stimulus. When these summed stimuli exceed a certain threshold, the animal drinks.

However, the double depletion hypothesis is considerably less useful when one has to find specific stimuli for extracellular and intracellular compartments. It is difficult to imagine what type of stimulus could represent 'cellular shrinkage' as such. Thus it was necessary to look more closely at this problem. The results of this examination, and the theories arising therefrom, are discussed elsewhere (see Chapter 15).

A similar situation arises when one considers the nature of extracellular mediators of thirst. As mentioned earlier, the venous side of the vascular system responds much more quickly than the arterial side to a change in blood volume. Thus it seemed reasonable to expect that the extracellular pressure or stretch receptors responsible would reside in the venous, possibly atrial side of the circulation. Some fairly recent work by Fitzsimons and his colleagues at Cambridge appears to corroborate this hypothesis (e.g. Fitzsimons and Moore-Gillon, 1980).

FIGURE 2.5 (b)



One known drinking stimulus, that of angiotensin, is not dealt with in this simulation. It is however incorporated in the larger model.

The intracellular and extracellular stimuli appear under most circumstances to be additive (Corbit, 1968; Fitzsimons and Oatley, 1968). An exception is that an overhydrated extracellular compartment will not inhibit drinking if the intracellular compartment is dehydrated. Thus the two stimuli are summed, and compared with a threshold value. If this threshold is exceeded, then drinking commences. Once drinking has started, the threshold is reset at a lower value; this ensures that drinking continues for an adequate period of time. This system is very similar in concept to that used by Toates and Oatley (1970). An 'oro-gastric metering' system has been included. The effect of this is as follows. As the animal drinks, an inhibitory stimulus to drinking accumulates. After some time, this can reach a sufficient strength to stop drinking. The strength of this inhibitory signal does not remain constant when drinking ceases; as time passes, it will slowly decrease. In addition, it does not merely decrease to normal. If adequate time passes, it can present a slight excitatory signal (in deference to Walter Cannon!)

The second 'peripheral' influence represented is an inhibitory effect due to the volume of water contained in the gastro-intestinal tract. The greater the volume, the greater the inhibition.

Both the functions described above are arbitrary, being loosely based on the data of Mook (1963), and Toates and

Oatley (1970). Thus there is no reason why the approach adopted should be the correct one. However, as will be shown in the next chapter, the predictions can be quite realistic.

### Feeding

The decision making system responsible for feeding is only intended as a rudimentary model, enabling the program to 'look after itself'. It may have some physiological relevance; however this was not the intention underlying its incorporation in the model, and should not be viewed with too critical an eye.

There are two major controls of feeding (see Figure 2.5(b)). First, and most frequently used is related to the size of the energy deficit between current metabolic needs and energy supply from food digestion. Thus eating patterns can be influenced within any period by metabolic rate or digestion rate. The second control is a more long-term device, that can induce eating if body energy reserves become sufficiently depleted. Both of the above stimuli can only be effective if there is room in the gut for food. Thus an excessive gut fill prevents eating. In a similar manner, too much water in the gut can prevent drinking. The volumes employed as upper limits are derived partly from Armstrong, Clarke and Coleman (1978), in their study of rats. As was mentioned earlier, this system should perhaps not be taken too seriously. The main aim of the model is to analyse water homeostasis; as such, energy regulation is ancillary to this aim.

Gastro- intestinal System

This system is comprised of the stomach and intestine. The function of the former is generally to act as a short-term storage, regulating an even flow of digesta to the intestine. In this latter component food is finally digested and absorbed into the body. Ingested fluids and inorganic ions are also absorbed. The role of the stomach is not entirely passive; some digestion and absorption does occur, but most takes place in the intestine.

The 'large rat' simulation incorporates a complex description of both stomach and intestine. In this simulation however, a somewhat contrasting approach is taken. To simplify matters, the stomach and intestine systems are treated as one. Constants determine the rate at which digesta are absorbed into the body from the gastrointestinal tract. These constants are derived from Armstrong, Clarke and Coleman (1978). Generally, the same is true for water and the principal electrolytes (Potassium and Sodium), although flow of these can also occur down concentration and osmotic gradients.

Thus this system has to deal with the intake and distribution of water, food, Sodium and Potassium ions. Although inter-related, the description of this system shall be divided into four further subsystems.

For simplicity, food ingested is treated as a single component, rather than the complex mixture of proteins, carbohydrates, etc. that it really is. Thus the rate of digestion is directly proportional to the amount of food in



the gastro-intestinal tract. This constant is derived from data produced by assuming a daily food intake of around 20 grams (actual intake is determined by the program), and data presented by Armstrong, Clarke and Coleman (1978).

Water uptake from the gut is also directly proportional to gut water content, but in this case the actual 'constant' is determined by the osmotic pressure gradient across the gut wall. Thus when dry food is ingested, the inorganic ion content of that food creates an osmotic pressure, drawing water from the plasma into the gut. This water is slowly reclaimed as the ions themselves are absorbed from the gut. Conversely, it follows that pure water, which exerts no osmotic effect, is absorbed most rapidly from the gut.

The absorption rate of Sodium and Potassium ions is directly proportional to gut contents of each ion. The transport of Sodium from the gut to the vascular compartment has been shown to be a linear function of intestinal Sodium concentration (Curran and Solomon, 1957). The constant used to determine the rate of uptake was determined empirically, using data from O'Kelly, Falk and Flint (1958). Ion input to the gut is normally as a consequence of their presence in food, but Sodium can optionally be input as a solution in the drinking water. This enables one to simulate the effects of drinking, for example, hypertonic saline.

Renal and Insensible Water Loss Subsystems

There are two major components of fluid loss from the body; urinary and 'insensible' (see Figure 2.6). The latter category can be further subdivided into losses via the lungs (pulmonary), skin and faeces. The animal can exert a considerable degree of control over its urinary loss, and thus is described first. Insensible water losses on the other hand are not so subject to regulation.

The rate at which plasma is filtered into the kidneys depends ultimately upon two factors; the net pressure tending to drive plasma across the glomerular membrane, from glomerulus to Bowman's capsule, and the permeability of the glomerular membrane (Guyton, 1976, p.443). Unless diseased, the latter is constant, and substances with a molecular weight of up to about 5,000 pass as freely as water. Thus any renal simulation has to be mostly concerned with calculating the various components of the net ultrafiltration pressure. As with Starling's capillary equilibrium (Starling, 1896; see later), the constituents are a combination of hydrostatic and osmotic pressures. Thus glomerular capillary pressure tends to increase glomerular filtration rate by driving plasma into the nephrons, whilst plasma colloid osmotic pressure and tubular pressure tend to reduce it. To have incorporated all of these factors in a model of this nature would have been impracticable. (They are however represented in the 'large rat'). Consequently, it was necessary to select a factor that most accurately reflects short-term changes in glomerular filtration rate.

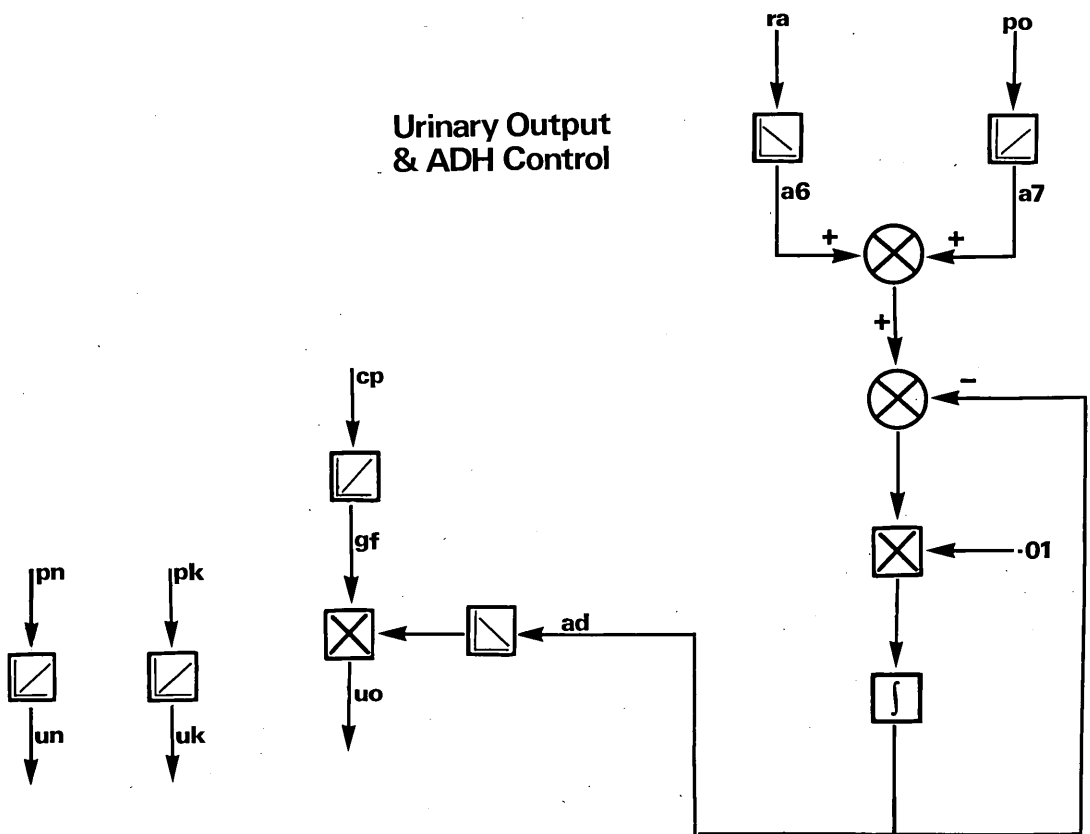


FIGURE 2.6

It was considered that the best candidate for this is glomerular capillary pressure. No published data is available to directly support this conjecture. However, Guyton and Coleman (1967) found that in the long term, glomerular filtration rate was closely correlated with arterial pressure. This latter factor is more likely to have influenced capillary than plasma colloid osmotic pressure. Thus whilst more complete models of glomerular filtration would incorporate all influences (e.g. Brenner (1976), and the 'large rat' description), it was felt appropriate in this case simply to use capillary pressure. The function relating capillary pressure to glomerular filtration rate here is a simple linear function, which is probably accurate enough for current purposes. Due to a lack of published information, the relationship was derived empirically, using physiological ranges of capillary pressure and glomerular filtration rate as the limits. Although this approach may leave much to be desired, it is felt that this is a more realistic representation than the use of arterial pressure alone as a determinant (e.g. Guyton and Coleman, 1967). In terms of the history of rat simulations, this model's predecessor (Toates, 1971) used extracellular fluid volume, there being no cardiovascular system. In physiological terms, this is something of a conceptual leap, far removed from the system currently being described. Predicted normal glomerular filtration rate is around .025 ml/s. This is in good agreement with published values. For example, Meredith (1957) gives a value of .025 ml/s for a 300g rat.

The proportion of glomerular filtrate that is

reabsorbed depends upon the plasma concentration of anti-diuretic hormone (ADH). ADH is released in response to any dehydrating stimulus; the greater its concentration, the greater the proportion of fluid reabsorbed from the kidney tubules, and hence urinary loss of fluid reduces. At the normal ADH concentration of 2.5 pg/ml, (Dunn et al, 1973), urinary output is .000295 ml/s, giving a daily output of around 25 ml. This is in reasonable agreement with published results, e.g. Collins (1978).

Guyton (1976, p.480) provides evidence, based on dog experiments, suggesting fundamentally different mechanisms for the regulation of extracellular Sodium relative to extracellular Potassium. It appears that Sodium concentrations are regulated by the ADH-thirst mechanism, whilst Potassium is largely regulated by the hormone aldosterone. The demonstration that the two regulatory systems can operate largely independent of each other has been exploited in the current simulation. Although in each case there is a hormonal mediator, there is a direct relationship between variations in plasma inorganic ion concentration and urinary output of that ion. Thus in this simulation, direct relationships between plasma Sodium, Potassium, and their respective urinary outputs have been derived. They were derived empirically, taking into consideration the physiological range of plasma concentrations, and the time taken for an infused load of ions to be cleared from the extracellular spaces by the renal system (Bia and DeFronzo, 1981). The latter factor gives an idea of the system's efficiency, or 'gain', when

presented with an eliciting stimulus. A system previously developed, that used plasma  $\text{Na}^+/\text{K}^+$  ratios to determine urinary outputs via aldosterone (as used by Guyton, Coleman and Granger, 1972), proved to be unreliable in this case. It is suspected that this was due to there being no control of acid- base balance.

There is a well-documented delay of about 45 minutes between an increase in plasma aldosterone concentrations, and the elicited increase in renal reabsorption (Guyton, 1976, p.462). Although the experiments cited appear to have been conducted in the dog, there appears to be no reason why the same should not apply in the rat. Consequently, there is incorporated in this program a delay of about this magnitude between a change in plasma Potassium concentration and a change in renal absorption of that ion.

Insensible Water Loss System

Insensible water loss, i.e. evaporative loss from the skin and lungs, can constitute a large proportion of water loss from a small animal such as the rat (Dicker and Nunn, 1957). Rats neither sweat nor pant (or at least very rarely; Collins and Bradshaw, 1973), and thus generally cool themselves by spreading saliva on their fur and skin. The importance of saliva for evaporative cooling is strikingly demonstrated by the poor tolerance to heat stress observed in desalivated rats (Hainsworth, 1967). The ability to withstand extremes of temperature is an important determinant of the geographical distribution of rodent species (Collins, 1978).

Thus it is not surprising that a positive relationship has been observed between salivary insensible water loss (SIWL) and ambient temperature in rats (Hainsworth, 1967, 1968). Although behaviourally mediated, there is a minimum level of SIWL below which the animal will not go. Thus neither food nor water deprivation eliminate SIWL (Macfarlane and Epstein, 1981). Under normal circumstances, SIWL accounts for 30 per cent of all insensible water loss in rats (Dicker and Nunn, 1957; Ritter and Epstein, 1974). These findings caused MacFarlane and Epstein (1981) to conclude that some elements of insensible water loss were under physiological, rather than behavioural control. There is also evidence to suggest that SIWL is significantly influenced by day phase, i.e., day or night (MacFarlane and Epstein, 1981).

Thus, to conclude, SIWL appears to be mainly determined by ambient temperature and day phase.

A second major contribution to overall insensible water loss is made by evaporation of water from the lungs, termed pulmonary IWL (PIWL). PIWL is significantly affected by a range of factors, such as relative humidity (Schmidt-Nielsen and Schmidt-Nielsen, 1950), ambient temperature (Hainsworth, 1967, 1968; Budgell, 1972), day phase (MacFarlane and Epstein, 1981), fluid deprivation (Dicker and Nunn, 1957; MacFarlane and Epstein, 1981), and age (MacFarlane and Epstein, 1982).

The reduction of PIWL that occurs during water deprivation (e.g. MacFarlane and Epstein, 1981) appears to be mediated by plasma concentrations of anti-diuretic hormone (Dicker and Nunn, 1957; Toates, 1971). In this simulation, losses of water via the faeces are ignored; rat faeces are very dry, and under normal circumstances faecal water loss does not vary greatly (Collins, 1978). In addition, age and relative humidity, known determinants of insensible water loss are not represented in the current model, as it has been assumed that these will, under normal circumstances, be constant.

In this simulation, the two relationships between ambient temperature, pulmonary and skin insensible water losses are combined into one general function, derived from Hainsworth et al (1968), and Semple (1952). This produces a good fit with experimental data, whilst keeping the system as compact as possible. The effects of day phase on overall insensible water loss are represented by including a phase-



related 'multiplier'. During the dark phase, this multiplier is greater than one. This, when applied to the predicted temperature/ IWL function described above, shifts the entire curve to the left, and achieves an appropriate value for predicted total IWL. The magnitude of this multiplier has been derived from MacFarlane and Epstein (1981).

Renin- Angiotensin System

The renin-angiotensin system is a complex hormonal system which plays a crucial role in cardiovascular and fluid regulation. Angiotensin is the most powerful vasoconstrictor known (Guyton, 1976, p.262); its effects are legion. Briefly, however, a decrease in either arterial pressure or extracellular Sodium content causes the kidneys to release renin. This in turn acts on one of the plasma proteins, renin substrate, to give angiotensin I. This is then converted, in the lungs, to angiotensin II. This latter substance has a number of important effects on the circulation related to arterial pressure control. First, it constricts the peripheral arterioles (this explains why in this simulation both angiotensin and autonomic activity influence arterial resistance to blood flow). Second, it causes a moderate constriction of the veins, thereby reducing the vascular volume, and also probably decreasing vascular compliance. Finally, it constricts the renal arterioles. This reduces blood flow through the kidneys, and hence urinary loss of both water and electrolytes (Guyton, 1976). For an introduction to this topic, see Vander, Sherman and Luciano, (1975).

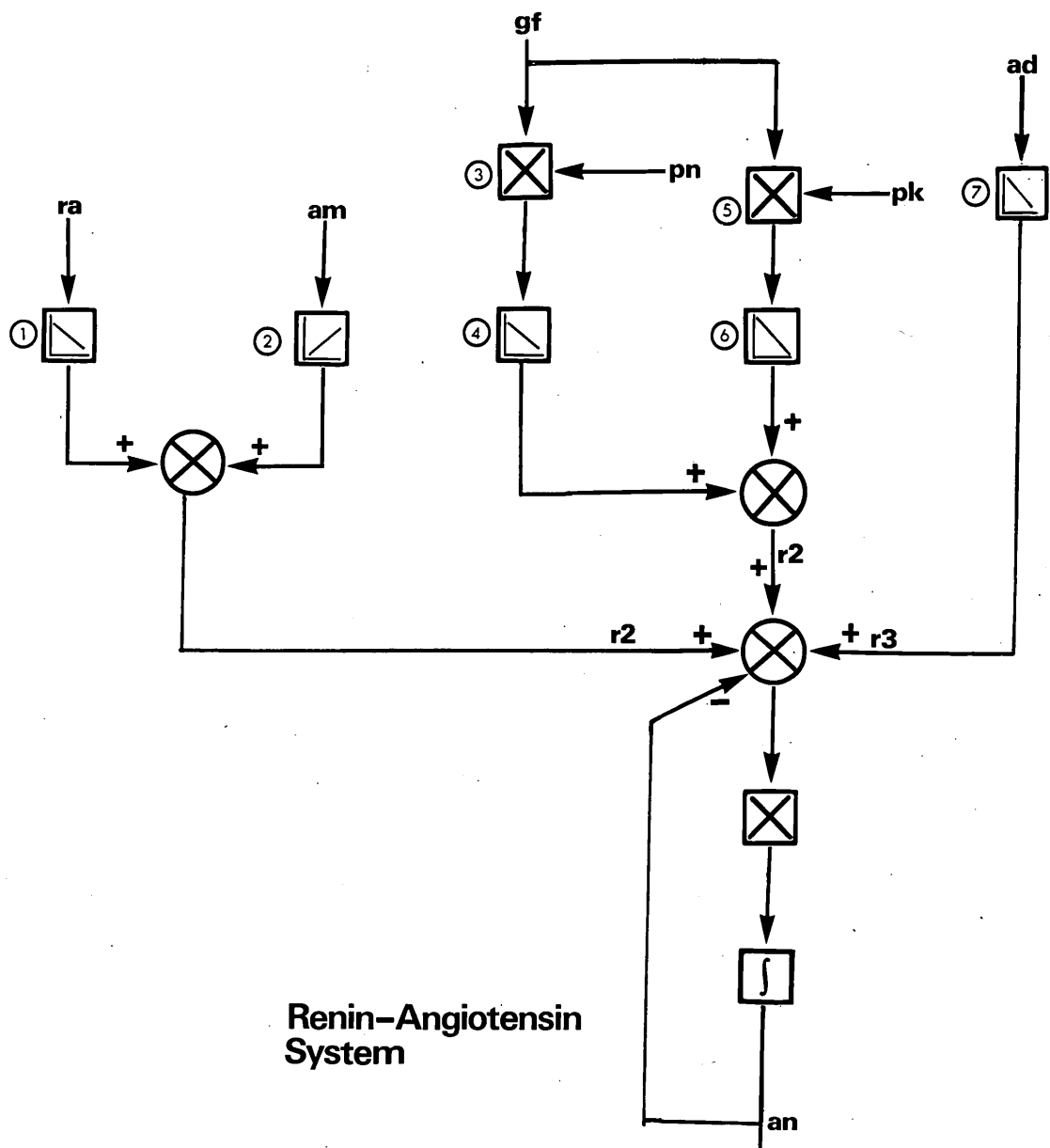
In addition, there is considerable evidence to suggest that angiotensin is capable of stimulating drinking (see FitzSimons, 1975, for a review).

In summary, a decrease in arterial pressure or Sodium stimulates the renin-angiotensin system, which via many influences acts to remove the deficit.

A large number of factors have been observed to influence the release of renin from the kidneys, and its subsequent conversion to angiotensin II (Guyton, 1976). Thus even the system presented here is a great simplification. For example, the actual conversion of renin to angiotensin I, then to angiotensin II, is a complex process. Here however, the relationship is assumed to be always direct, with no possibility of amendment. Nevertheless, it is felt that even a system such as this can provide one with a valuable insight to the metabolism of renin and angiotensin. The system is shown in Figure 2.7.

Brosnihan and Bravo (1978) showed that graded reductions in arterial pressure causes increases in renin secretion, without corresponding changes in arterial pressure. This suggests an atrial role in plasma renin regulation. This is not particularly surprising, as the venous side of the circulation is generally the first to detect variations in blood volume, and it makes sense to have detecting systems in the most sensitive sites. Thus block 1 shows the relationship between right atrial pressure and the release of renin (from the kidneys). The relationship is derived from dog studies by Brennan, Malvin, Jochim and Roberts (1971), and Brosnihan and Bravo (1978). No corresponding data exists for rats.

Guyton (1976, p.469) gave autonomic excitation of the renal nerves as a principal cause of renin release. Later, Ammons et al (1980) demonstrated the role of carotid baroreceptors in regulating plasma renin levels. Thus it seemed reasonable to include an autonomic effect on renin



Renin-Angiotensin System

FIGURE 2.7

release in this simulation. Cunningham et al (1978- dogs) showed that a moderate fall in arterial pressure induces the release of renin. Somewhat tentatively, this has been assumed to be due to autonomic influences (the autonomic system is largely 'driven', in this respect, by arterial receptors). This effect is shown in block 2.

Renal factors are also believed to influence the release of renin. It appears that an important determinant of renin release is the exposure of the renal macula densa cells to variations in plasma Sodium load (Blaine et al, 1972; Davis and Freeman, 1976). In addition, it has been shown that the plasma load of Potassium tends to counteract the effects of Sodium (Abbrecht and Vander, 1970; Brunner et al, 1970). These changes can all be independent of any changes in renal haemodynamics. There is much debate about the actual renal site responsible for regulation of renin release (e.g. Davis and Freeman, 1976), but fortunately this is at too reductionist a level to concern the present simulation. At any rate, renal Sodium and Potassium loads are of critical importance (Vander, 1967). Thus blocks 3 to 6 calculate the rate at which these two electrolytes flow through the kidneys, by multiplying glomerular filtration by their respective plasma concentrations. Block 4 represents a highly speculative relationship between renal Sodium load and renin release; block 6 performs the analogous task for Potassium load. Although arrived at independently, this approach is similar to that taken by Blaine, Davis and Harris (1972).

Plasma anti-diuretic hormone (ADH), amongst other

influences, has been shown to exert an inhibitory effect on renin release (e.g. Shade, Davis et al 1973). This tendency is represented in block 7. Again, the function used is somewhat speculative.

Due to a general shortage of information, each of the five influences on renin release described here are given an equal effect. This may not of course be the case, but at least it does not pretend to give accuracy where there is none.

All the effects are assumed to be additive. There are reasonable grounds for this assumption, although one must be wary as the relevant studies were conducted on the ADH system (Johnson, Zehr and Moore, 1970). Finally, the summed effects are subjected to an exponential delay. The aim of this is to simulate the delay that occurs between a change in plasma renin activity and the consequent change in angiotensin II concentration.

Anti- Diuretic Hormone Control

Anti-diuretic hormone (ADH) is responsible for determining the amount of water reabsorbed from the kidney tubules. The greater the plasma concentration of ADH, the greater the proportion reabsorbed, reducing urinary loss. Thus it forms a vital part of overall body fluid regulation.

The stimuli subserving ADH release fall into two categories; those responding to changes in plasma osmolality, and those responding to changes in blood volume.

The osmoreceptors responsible for ADH release are situated in the hypothalamus, probably in a perinuclear region of the supraoptic area (Leng, Mason and Dyer, 1982). When body fluids are concentrated, the supraoptic nuclei become excited, and impulses to the pituitary, from which ADH is secreted (Guyton, 1976).

The issue is less clear when considering the analogous systemic receptors responsible for ADH release. Generally, as Guyton (1976) states;

"The increased secretion is believed to result mainly from the low pressure caused in the atria of the heart by the low blood volume. The relaxation of the atrial stretch receptors supposedly elicits the increase in ADH secretion. However, the baroreceptors of the carotid, aortic and pulmonary regions also participate in this control of ADH secretion." (Guyton, 1976, p.1001).

Furthermore, as Vander et al (1975, p.337) point out, the relevant atrial receptors are predominantly grouped in the left atrium.

The various determinants of ADH secretion appear to be additive in nature (Reeve and Kulhanek, 1967). Johnson, Zehr and Moore (1970) studied the effects of small changes in plasma osmolality and volume in sheep. They found that provided interventions were within physiological limits, neither osmo- nor baro-receptors dominated. When combined, the effects were roughly additive.

In this simulation, plasma ADH concentration is regulated by right atrial pressure and plasma osmolality. Johnson, Moore and Segar (1969) showed that increases in left atrial transmural pressure induced a reduction in plasma ADH concentration. A year earlier, Henry et al (1968-dogs) had shown that non-hypotensive acute haemorrhage, which could only stimulate low pressure receptors, caused an increase in ADH concentration. One is tempted to suspect that the same left atrial pressure receptors are involved. This is not to say that arterial receptors cannot affect ADH; it is just that they do not under normal circumstances, as the low pressure venous system will detect a change long before the high pressure arterial system.

Thus just one problem remains. Left atrial pressure is not determined in this simulation; can one be justified in assuming that right atrial pressure is a reasonable analogue to left atrial pressure? Fortunately, some information is available on this subject. Henry, Gauer and Sieker (1956) showed in the dog that left atrial pressure paralleled right



atrial pressure over a wide range of estimated blood volumes. Thus one can relate ADH concentration to right atrial pressure with some certainty.

The relationship between plasma osmolality and ADH concentration appears to be linear, in both human (Schrier, Berl & Anderson, 1979) and rat (Dunn et al, 1973). There is some dissent on this issue; for example Weitzman and Fisher (1977) suggest that the relationship is exponential, rather than linear. However Rodbard and Munsen (1978) re-analysed Weitzman and Fisher's (1977) data, and concluded that their results can be compatible with either a linear or exponential model. I have not come across any counter arguments claiming that the 'linear' data produced by other authors is also compatible with an exponential model, which of course they may be. However, it is apparent that at least within the normal physiological ranges of plasma osmolality, the relationship with plasma ADH concentration is linear. Not surprisingly, there appear to be species differences in osmotic threshold.

There is conflicting evidence about whether or not angiotensin stimulates ADH secretion. This phenomenon was originally suggested by Bonjour and Malvin (1970), and Ramsay et al (1978) derived a dose-response curve between angiotensin and ADH. Cadnapaphornchai et al (1975) had searched in vain for such a relationship, however. Considering the wide range of effects exerted by angiotensin, one can never be certain that the observed effects of angiotensin on ADH are direct, and do not occur as a side-effect of its action on another system. At any

rate, it was felt that to incorporate such a relationship in the current simulation was not entirely justified.

The summed effects of right atrial pressure and plasma osmolality are in this simulation subjected to a delay; this is to simulate the time taken for an increase in secretion rate to be reflected in plasma concentration. The extent of this delay was calculated empirically, using data from Dunn et al (1973) and the 'large rat' simulation. Following a stimulus, half the equilibrium concentration would be achieved in several minutes.

Normal plasma concentration is around 2.2 pg/ml, which corresponds to the radio-immunoassay studies of Kleeman and Vorherr (1974), (3 pg/ml) and Dunn et al (1973), (2-5 pg/ml-rats). The latter authors state that severe dehydration increases ADH concentration by a factor of around 10. These data are considered to be more reliable than earlier studies, based on bioassay of anaesthetised rats; here, plasma concentrations of up to 500 pg/ml were found in the rat.

The system representing ADH metabolism is shown in Figure 2.6. The functions relating atrial pressure and plasma osmolality are best-fit curves to data provided by Dunn et al (1973- rats), Johnson Moore and Segar (1969-dog), and Henry et al (1968- dog). It is unfortunately necessary to assume that approximately the same relationships hold in the rat as in the dog.

Autonomic Nervous System Control

This is the part of the nervous system that controls the visceral functions of the body. Thus it has a crucial part to play in the regulation of arterial pressure (by a number of means), gastro-intestinal motility, hormone secretion, renal dynamics, and many other activities.

The autonomic nervous system is activated mainly by centres located in the spinal cord, brain stem and hypothalamus. It can also be influenced by some 'higher' areas of the brain, such as the cerebral cortex. Signals from the autonomic system are transmitted to all parts of the body through two major subdivisions, the sympathetic and parasympathetic. The interaction of these two subsystems can be quite complex; there is no generalisation one can use to explain whether sympathetic or parasympathetic stimulation will cause excitation or inhibition of a particular organ (Guyton, 1976, p.773). The two systems occasionally act reciprocally to each other. However, most organs are predominantly controlled by one or the other of the two systems, so that they do not normally oppose each other.

In this simulation, the autonomic influences of greatest importance are those pertaining to cardiovascular regulation, and the release of hormones. These are largely controlled by the sympathetic branch of the autonomic system. An increase in sympathetic activity serves to increase heart rate and constrict systemic vessels. Both of these effects increase arterial pressure, and thus help to

maintain adequate tissue perfusion during periods of hypovolemia, as would happen during, say, following haemorrhage. In common with other simulations in which autonomic activity is represented (see the corresponding section in the 'large rat' simulation), autonomic activity is treated as a unitary phenomenon. It does not consider such aspects of autonomic behaviour as reciprocal innervation.

The system developed for use in this simulation is naturally a gross simplification of reality, but still acts in a reasonably realistic manner. The term 'autonomic multiplier', referring to the degree of excitation produced by the autonomic nervous system, is borrowed from Guyton and Coleman (1967). One example of the simplifications present here is the use of arterial baroreceptors alone to determine autonomic activity. There is ample evidence to suggest that there are also chemoreceptor, atrial stretch receptor and hormonal influences; all of which are lumped into one function related to arterial pressure. However, some care has been taken to ensure that such characteristics as stimulus-response latency and baroreceptor adaptation are reasonably accurately represented. It was felt that a complex representation of autonomic dynamics was not appropriate in this simulation, considering the necessity for a compact design. The 'large rat', on the other hand, probably contains the most complete representation available in a simulation of this type. The smaller system employed in this simulation is illustrated in Figure 2.8.

Block 1 derives from arterial pressure the essential

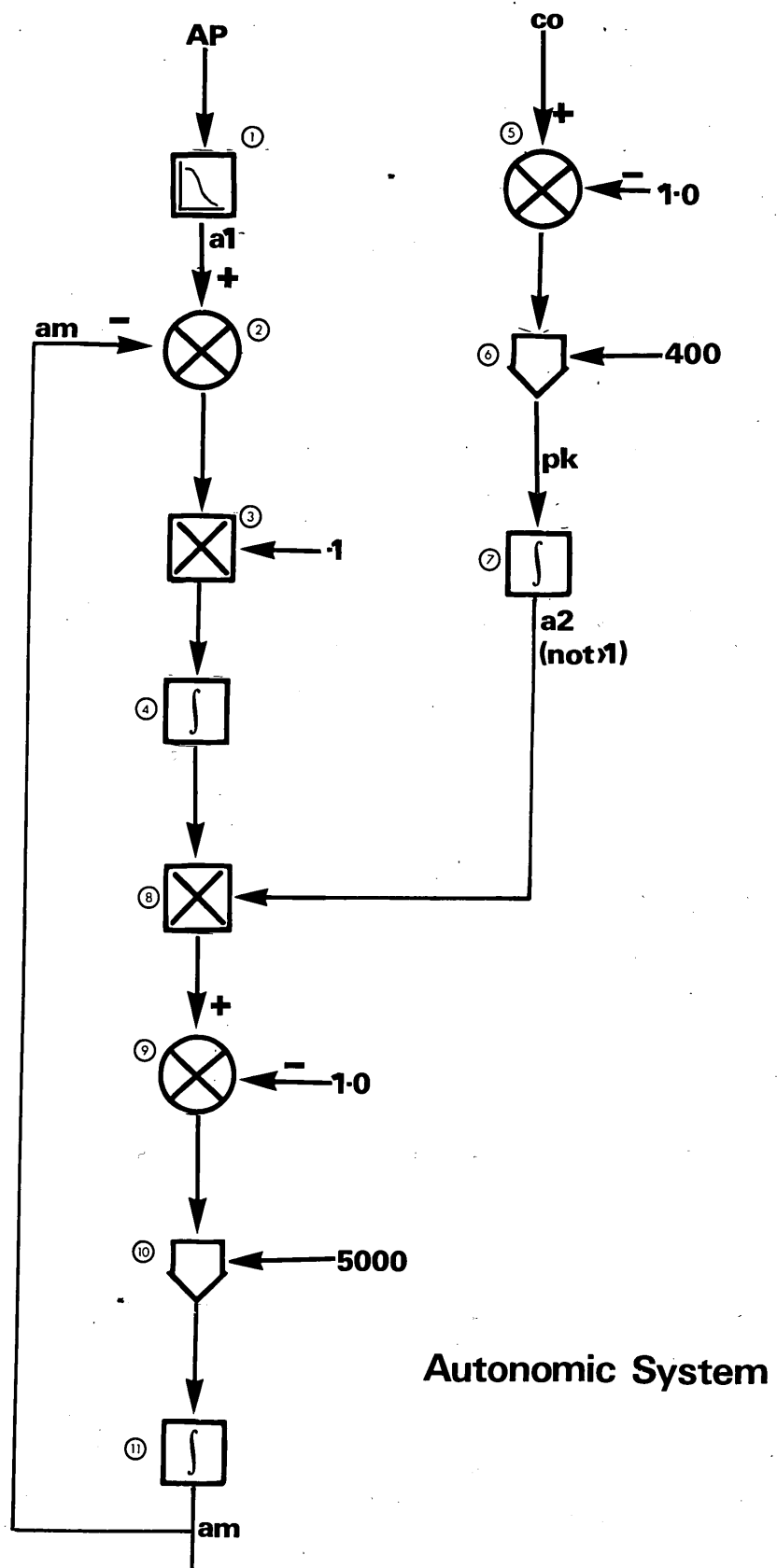


FIGURE 2.8

driving stimulus for the whole system. The relationship used is based on data provided by Spickler and Kezdi (1967- dogs) and Koushanpour and McGee (1969- dogs). Unfortunately, no direct rat evidence is available, this animal being too small for such types of experimentation.

Blocks 2,3 and 4 represent an exponential delay, the function of which is to simulate the stimulus-response latency demonstrated by arterial baroreceptors. This is based on data given in Guyton (1976), p.276.

Blocks 5 to 7 represent the effects of cns ischaemia resulting from inadequate perfusion of the brain. Blocks 5 and 6 produce a small negative signal when cardiac output is less than .7 ml/s (normal is around 1.44 ml/s for a 300g rat). This signal is integrated in block 7 to produce variable a2. This variable is not allowed to exceed one. Thus when block 8 multiplies the output of block 4 by a2, the effect of ischaemia may be to reduce the ability of the autonomic system to respond. As the value of a2 cannot be greater than one however, it can never increase the ability of the autonomic system. This system is particularly important in the simulation of haemorrhage, where the failure of adequate brain perfusion limits the animal's ability to recover, and is the normal cause of death following severe haemorrhage. All the constants employed in this system have been empirically derived. As is shown by some of the simulations presented later, it has proven to be remarkably realistic.

It has been found that during constant stimulation over a number of days, the baroreceptors initially respond in the

appropriate direction, but then gradually 'reset', tending back towards their previous, normal levels. (Guyton, 1976; Cowley and DeClue, 1976; McCubbin et al, 1956). This tendency is represented in Figure 2.8 by blocks 9 to 11. Over a period of several days, this system will operate so as to restore autonomic activity to normal (1.0), whichever the direction of the initial disturbance.

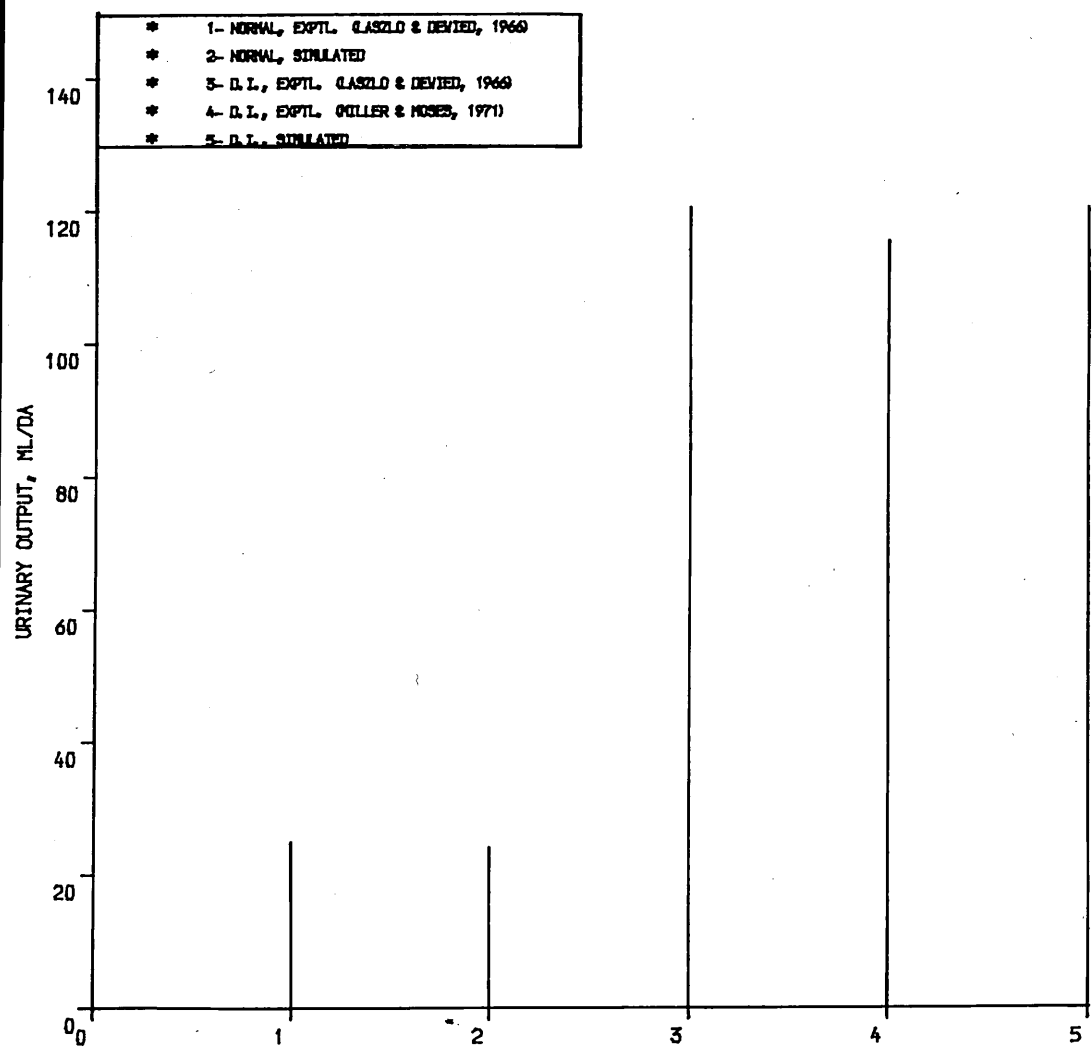
CHAPTER 3Simulations Conducted with the 'Small Rat'Diabetes Insipidus

This simulation, using the 'small rat', studies the effect on drinking and urinary output of an absence of anti-diuretic hormone (ADH). This clinically-observed phenomenon demonstrates itself by the production of large amounts of urine, containing low concentrations of inorganic ions. As other regulatory systems are acting to maintain body Potassium and Sodium levels, most of these ions appearing in the glomerular filtrate are reabsorbed, and hence the urine is normally hypotonic.

The experiment was conducted for a simulated time of three days, during which period food was available 'ad lib'. Figure 3.1 illustrates the dramatic effect that abolition of ADH has on urinary output. Normal urinary output is about 20 ml/day for a 300g rat, as shown. Simulated daily water intake was about 28 ml; given an average simulated insensible water loss of just over 6 ml/day, it can be seen that the system is capable of 'behaving itself' under normal circumstances. Daily food intake was about 25 g. When the influence of ADH is removed however, urinary output rises to about 120 ml/day. In order to prevent dehydration, water intake increases to a corresponding degree.

On the other hand, in DI rats urinary output of Sodium and Potassium remain essentially similar to normal rats. In both cases Potassium excretion greatly exceeded that of Sodium; this is because the food presented to the animal is





DAILY URINARY OUTPUT OF NORMAL AND D. I. RATS

FIGURE 3.1

particularly high in Potassium. The food constitution is derived from that of a standard laboratory dried rat food (Toates, 1971); the same food is presented to the large simulation, discussed elsewhere.

It is interesting to note that in day 1 the simulated DI rat showed an excessive loss of Sodium (about 30 mg). This can be attributed to a loss of extracellular fluid, whilst the simulation reaches a new equilibrium. In day one, urinary loss of water exceeded that drunk by about 10 ml, and the brunt of this loss would have been borne by the extracellular compartments. To date no experimental findings have come to light indicating the validity or otherwise of this prediction. Provided an experiment could be constructed, it would be interesting to test this hypothesis.

Laszlo and DeWied (1966) induced diabetes insipidus in normal rats by surgically lesioning the pituitary stalk, which plays a role in ADH metabolism. Following this surgical treatment, daily urinary output increases from around 23 ml to about 120 ml, which is in close agreement with the predictions of the model. Alternatively, Miller and Moses (1971) studied rats whose diabetes insipidus is inherited, the Brattleboro strain. Animals that are homozygous for DI have a complete deficiency in the ability to synthesise and release ADH. The daily urinary output of water by these rats is around 110 and 120 ml, which again is in good agreement with the predictions of the model.

It is interesting to note that Brattleboro rats homozygous for DI are in fact capable of concentrating their

urine (to around 600 mOsmoles/l compared with plasma osmolality of 300 mOsmoles/l) during fluid deprivation (Gellai, Edwards and Valtin, 1979). This is possibly related to the concomitant reduction in glomerular filtration rate. The link with GFR is suggested somewhat tentatively, because Edwards, Gellai and Valtin (1980) have shown that Brattleboro rats can, when water-deprived, excrete hypertonic urine with minimal or no change in glomerular filtration rate. Obviously, much still remains to be discovered. It is considered possible that this is due to increases in circulating angiotensin levels. Angiotensin has been shown to influence glomerular filtration rate (Malvin and Vander, 1967), presumably by constricting renal arterioles. Increases in plasma colloid osmotic pressure would also affect filtration rate. Presently however, the means by which the DI rat achieves this is unknown. It is considered unlikely that any of the simulations presented here could emulate such a phenomenon.

Haemorrhage

Although haemorrhage is an acknowledged stimulus to drinking, the main aim of this particular simulation was to study the cardiovascular and autonomic responses to haemorrhages of varying sizes, in order to assess the validity of the assumptions underlying the model.

The model's responses to haemorrhages of various sizes are shown in Figure 3.2.

Guyton and Crowell (1961) showed a series of graphs illustrating the course of arterial pressure after different degrees of acute haemorrhage. (See also Guyton 1976, p.359). Although conducted in dogs, there is no reason to suspect that the rat responds in any different way. The results of Guyton's work, shown in Figure 3.3, are clearly very similar to those predicted by this simulation. Following a small (3 ml) acute haemorrhage (Figure 3.2), the rapid drop in arterial pressure induces an increase in autonomic activity. This increases vasomotor tone and peripheral resistance to blood flow, which in conjunction with the increase in heart activity acts to restore an adequate perfusion pressure. With such a small haemorrhage, much of the plasma lost can be replaced by the trans-capillary flow of free interstitial fluid. This occurs automatically, as a consequence of the reduced capillary pressure causing an imbalanced capillary filtration, as predicted by Starling's law.

The situation facing the average rat after haemorrhages of 5.25 and 5.5 ml (Figure 3.2) is more severe. Here, the

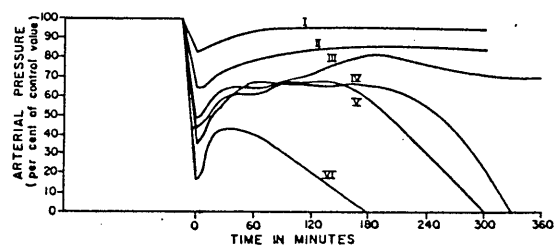
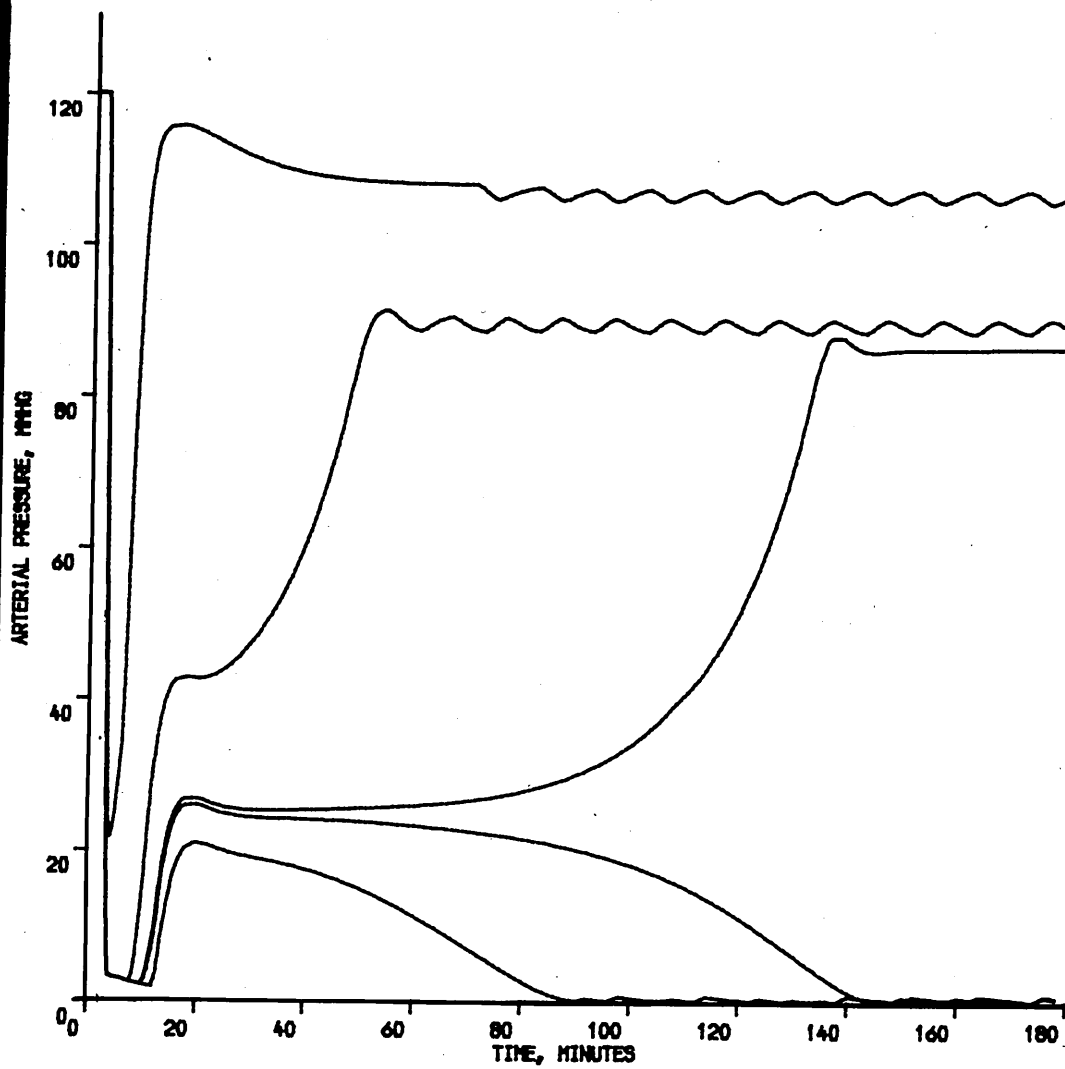


Figure 3.3- Course of arterial pressure in dogs after different degrees of acute haemorrhage.

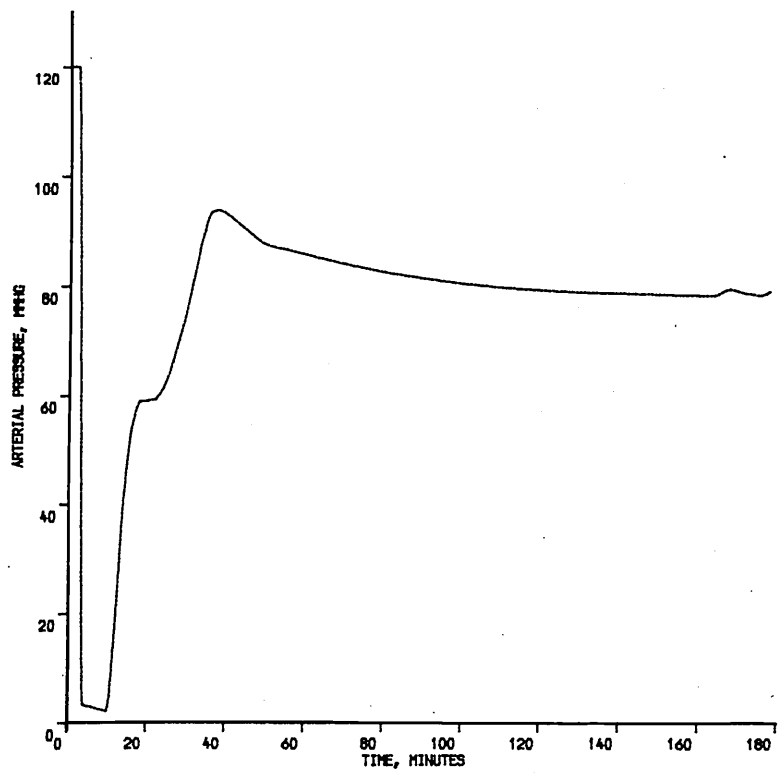


SIMULATED RESPONSES TO HAEMORRHAGES

FIGURE 3.2

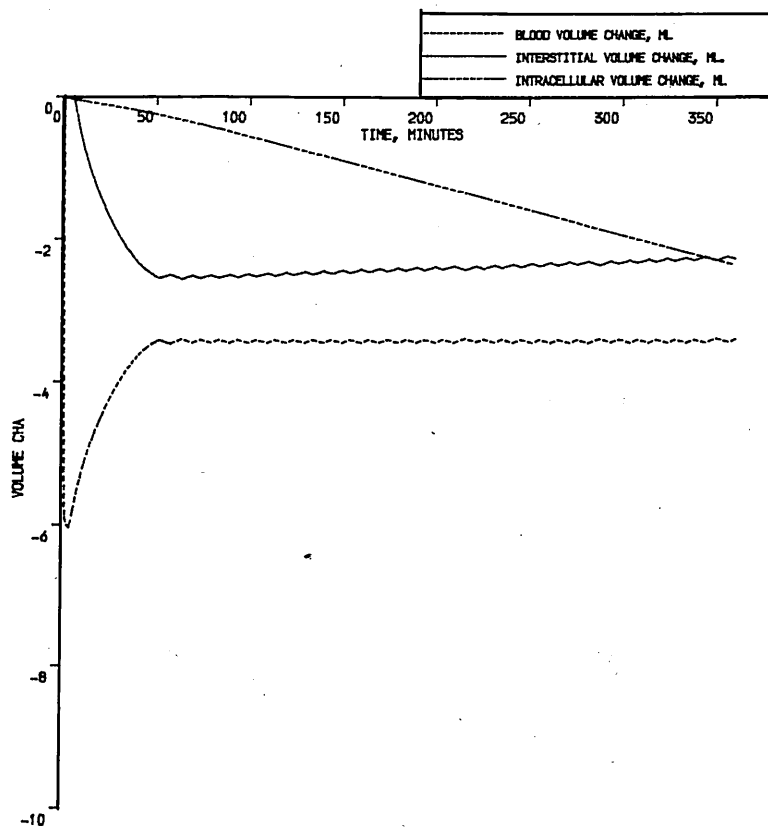
period of reduced arterial pressure is protracted, and initiates the 'C.N.S. ischaemic response' (Dampney et al, 1979; Dampney and Moon, 1980). This is an extreme autonomic response initiated by hypoxia of particular areas of the brain (Dampney and Moon, 1980- rabbit), and is very much a 'last resort' mechanism. In Figure 3.2, it can be seen that the response following the 5.5 ml haemorrhage only just succeeds in maintaining life. Continued hypoxia, despite the efforts of the C.N.S. ischaemic response, results in the impairment of neural (and hence autonomic) activity. Should this impairment be sufficiently severe to prevent the autonomic system from maintaining an adequate blood flow, then the animal will be caught in a 'vicious circle' of irreversible shock. At this stage, even transfusion may not save the animal if neuronal activity is severely curtailed. This situation can be seen in Figure 3.2, after the 5.7 ml haemorrhage. Here, despite the strong autonomic response, the initial drop in arterial pressure is so profound as to severely impair neuronal activity, and the system eventually collapses.

It can be seen that provided the degree of haemorrhage is no greater than a certain critical amount, the cardiovascular system will be able to cope. Exceeding this critical level, by even very small volumes, will eventually lead to deterioration and death. As has been suggested elsewhere in this volume, the relative availability of free interstitial fluid may often make the difference between recovering after a haemorrhage (non-progressive shock) and eventual failure (progressive shock), in which the shock



SIMULATED 7.5ML HAEMORRHAGE- WATER AVAILABLE

FIGURES 3.4 & 3.5



COMPARTMENT RESPONSES TO 5.5ML HAEMORRHAGE



itself causes still more shock. During progressive shock, it is apparent that inadequate interstitial fluid is available to flow into the cardiovascular spaces, and thus plasma volume falls below the critical level. Presumably, the same argument would apply to water contained within the gastrointestinal tract.

It was mentioned earlier that haemorrhage can act as a potent stimulus to drinking. That this response is beneficial can be seen in Figure 3.4. Here, a haemorrhage that would rapidly kill the animal denied access to water is easily survived. In effect, the infused (gastric- 10 ml) water acts as a rapid infusion, acting before the onset of irreversible shock. This situation closely parallels experimental studies of the effect of transfusions following haemorrhage in dogs (Guyton and Crowell, 1961).

There is a sharp reduction in urinary output of water by the simulation following a moderate haemorrhage. This can be attributed to two causes. First, glomerular filtration rate drops, due to the lower renal perfusion pressure (Selkurt, 1945- dogs); this in turn is due to the reduced arterial pressures, and probably, vasoconstriction of the renal arterioles by increased levels of circulating angiotensin (Cousineau, Gagnon and Sirois, 1973; Claybaugh and Share, 1973; Regoli and Vane, 1966). Second, the drop in arterial and venous pressures induces a release of anti-diuretic hormone, promoting renal tubular reabsorption of water. In the case of a slight haemorrhage, ADH release will most probably be mediated by a decrease of venous pressure, as this is less well 'defended' by the cardiovascular system

than is arterial pressure (Gupta, Henry et al, 1966). Following a severe haemorrhage however, even arterial pressure cannot be adequately maintained, and thus both arterial and venous receptors elicit a release of ADH. As a consequence, it is perhaps not surprising that urinary output drops greatly. The response of this simulation is very similar to that seen by Phillips, Dole, et al (1945-human) and Borst (1948-human). Generally, there is an almost complete cessation of urine flow, followed by a partial recovery of function, the extent of which depends on the severity of haemorrhage. Unfortunately, no data has yet come to light that permits a direct comparison of predicted and experimental results, so no graphical presentation is offered.

Stewart and Rourke (1936) report that the intracellular compartment reduces slightly following haemorrhage; their evidence for this being a relative increase in urinary Potassium. The reasons for this are even now somewhat uncertain, but it is interesting to note that the same response appears in this simulation (Figure 3.5). Similarly, the human data from Borst (1948) suggests increased urinary Potassium; certainly plasma Potassium levels are significantly increased. It is also interesting to note that he reports increased urinary Potassium output during dehydration. In this simulation, it is suspected that the gradual increase in urinary Potassium after about 4 hours is due to the catabolism of intracellular energy stores, in order to fulfil energy requirements; throughout the experiment no food is available. However, perhaps a note of

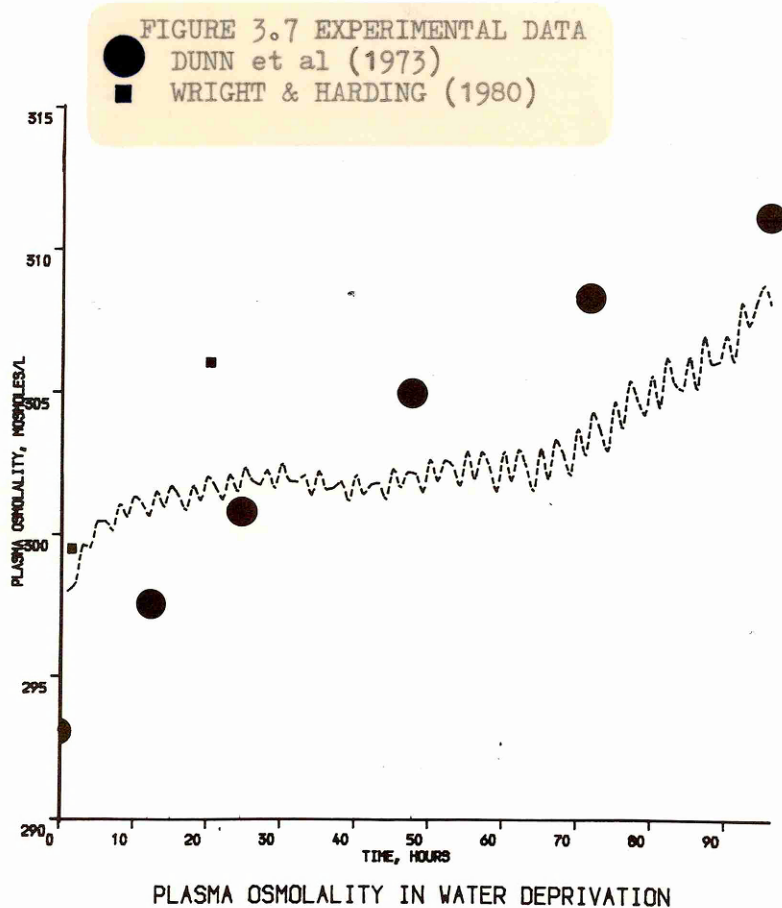
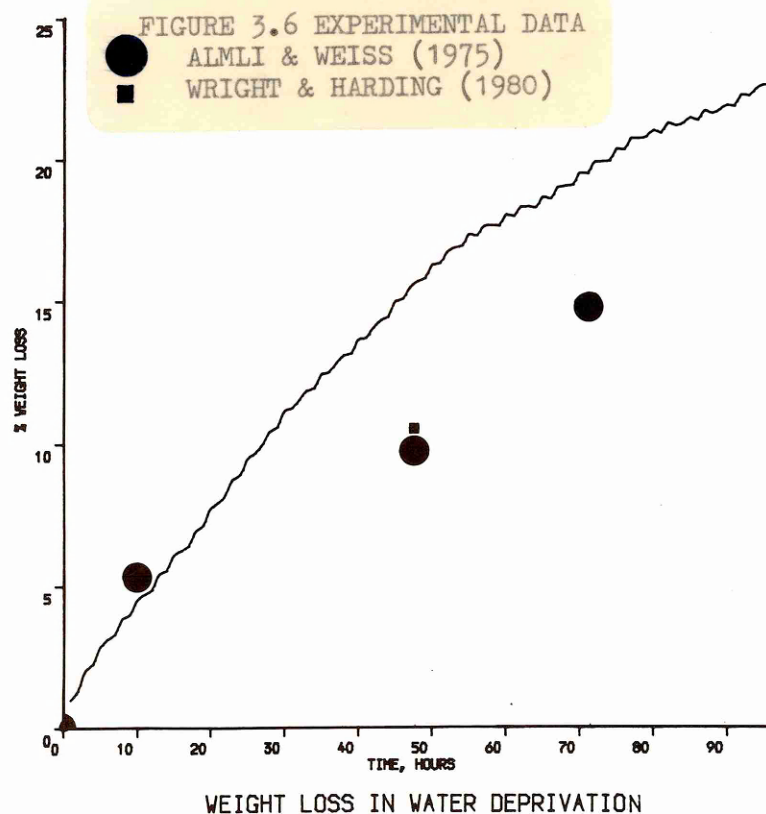
caution should be added here; there is evidence to suggest that some at least of the intracellular Potassium losses during dehydration may be stress-related. This topic is discussed in greater depth in Chapter 7.

Figure 3.5 shows the contributions made by each of the two other body fluid compartments in an attempt to restore an adequate volume in the third following a haemorrhage. As would be expected, most of the fluid is contributed by the interstitial compartment; hence the considerable importance of the availability of free interstitial fluid in determining survival following haemorrhage. This response appears to be realistic; there is much evidence to suggest that interstitial fluid transport has an important role to play in shock (Adolph, Gerbasi and Lepore, 1933; Koven et al, 1970, 1972). The reason for the slight restoration of interstitial fluid volume is uncertain. Perhaps it is related to the gradual loss of intracellular fluid, alluded to earlier in this discussion. That there is a loss of intracellular fluid is clear from Figure 3.5. Naturally, the absolute loss is not great, for the total loss of plasma was only about 4 ml, and this can hardly be expected to have a great effect on a compartment whose normal volume is around 145 ml. In addition, it would be anticipated that some of the fluid loss from the intracellular compartment would occur as a consequence of energy store depletion, as no food is provided during the experiment.

The Effects of Water Deprivation

The effects of water deprivation (with 'ad lib' food) on the 'small rat' simulation are shown in Figures 3.6 to 3.9. The period of deprivation is 4 days. As the supply of energy from the gastro-intestinal tract is small, the animal's energy requirements have to be met from intracellular energy stores. In the larger simulation, described later, these reserves consist of independent glycogen, fat and protein. In this simulation, however, they are all subsumed under one category (see Chapter 2). The general assumption is made that each gram of energy store is associated with 3 grams (ml) of water. Obviously the water released subsequent to oxidation of energy reserves arises from several sources. First, there is water chemically bound to the substrate, released as a consequence of its chemical breakdown. Second, there is the water more loosely held; thus glycogen is thought to be associated with three times its weight of water. This too is released when the substrate is metabolised (e.g. Bintz and Mackin, 1980).

The water released, in effect as a consequence of the reduction in size of the intracellular compartment, flows into the interstitial, and thence the cardiovascular compartments. The fluid flow however is insufficient to prevent extracellular dehydration; obligatory urinary output and insensible water loss combined exceed this flow. This phenomenon, predicted by the simulation presented here, has frequently been observed (e.g. Dunn et al, 1973) in laboratory rats. Bintz and Mackin (1980) have shown that

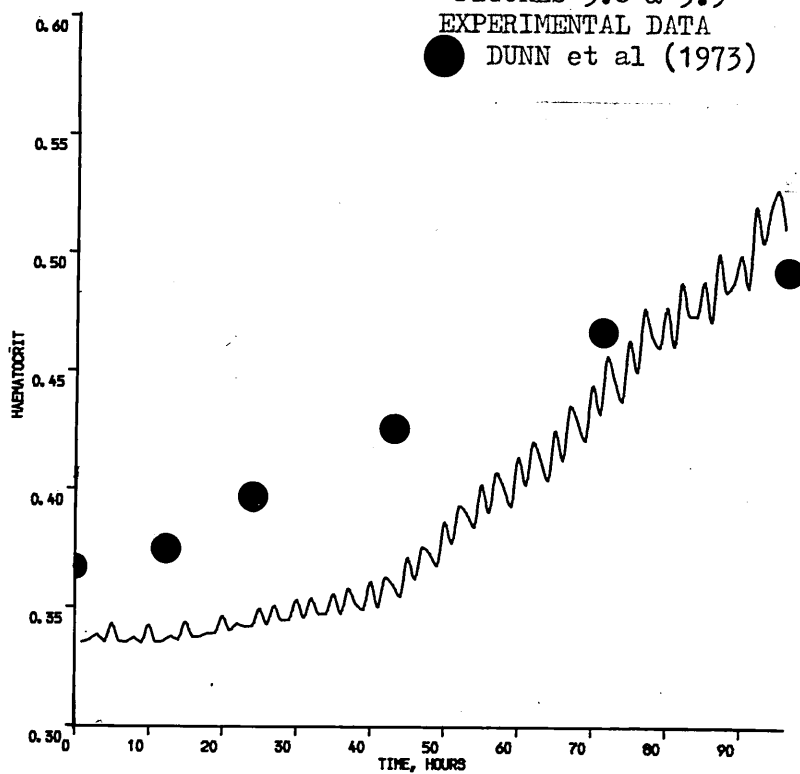


more efficient animals, such as Richardson's ground squirrels, can in fact remain in water balance during food and water deprivation. Thus although the intracellular compartment reduces (in much the same way as in this simulation), and the animal loses weight, the water content of body constituents does not decline; indeed, that of adipose tissue increases slightly. Figure 3.6 shows the weight losses incurred by both simulated and experimental rats over a four day period of water deprivation. During this time, very little food is eaten- about 8 grams was given to the simulation per day, compared with a normal simulated intake of about 25 g. The experimental points offered for comparison are from Almlie and Weiss (1975) and Wright and Harding (1980). Most of the weight loss incurred by the simulation was as a consequence of intracellular energy store depletion, with concomitant release of intracellular fluid.

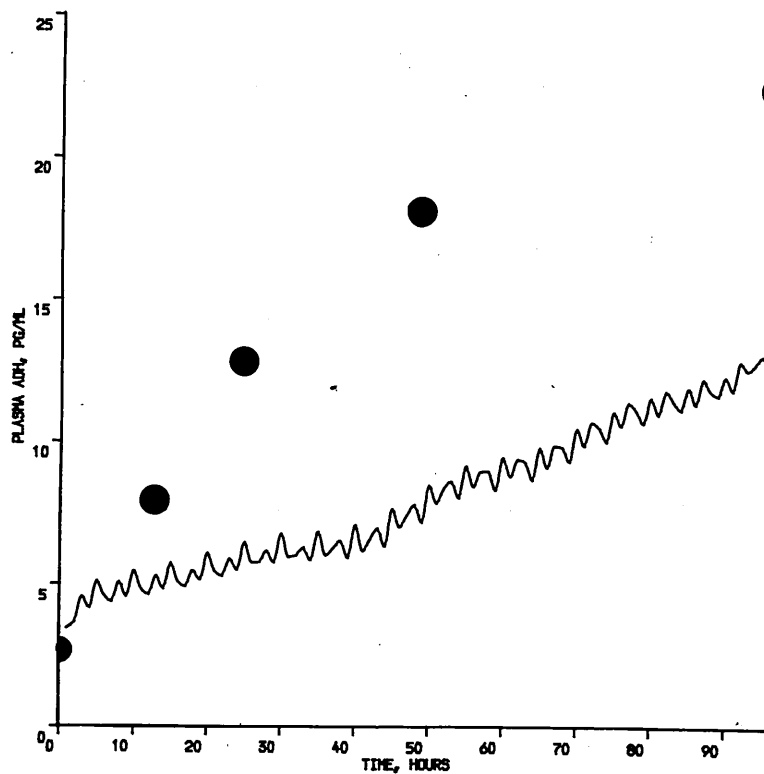
As would be expected, the plasma concentrations of electrolytes and anti-diuretic hormone increase during dehydration. The simulated results are shown in Figure 3.7; experimental points are also shown, for comparison (Dunn et al, 1973). Whilst the general trends of predicted and experimental results are the same, it appears that the simulation is a little too efficient at maintaining plasma osmolality. Nevertheless, for a relatively crude simulation, the results are encouraging. Most of this increase in osmolality is a consequence of increased plasma Sodium.

The ratio of red blood cell volume to total blood volume ('haematocrit') is generally regarded as a good

FIGURES 3.8 & 3.9  
EXPERIMENTAL DATA  
● DUNN et al (1973)



HAEMATOCRIT IN WATER DEPRIVATION



PLASMA ADH IN WATER DEPRIVATION

indicator of extracellular hydrational state. Thus simulated and experimental results are shown in Figure 3.8. It can be seen that they are in reasonable agreement, although the experimental data seems to indicate that the most rapid loss of extracellular fluid is during the first two or three days of fluid deprivation. The experimental data are derived from Dunn et al (1973).

The classic works of Verney (e.g. 1947) have shown that changes in plasma osmolality act as a potent stimulus to the release of antidiuretic hormone. Thus Figure 3.9 shows the predicted and experimental increases in plasma ADH concentrations during four days of water deprivation. Obviously, whilst basal levels are in good agreement, the model does not react as strongly as the real thing (all comparisons given here are with rats). It remains to be seen whether the 'dose-response curve' of the simulation is more sensitive than experiments suggest, to counteract the relatively minor changes in plasma ADH.



A Study of 'Sham-Drinking'

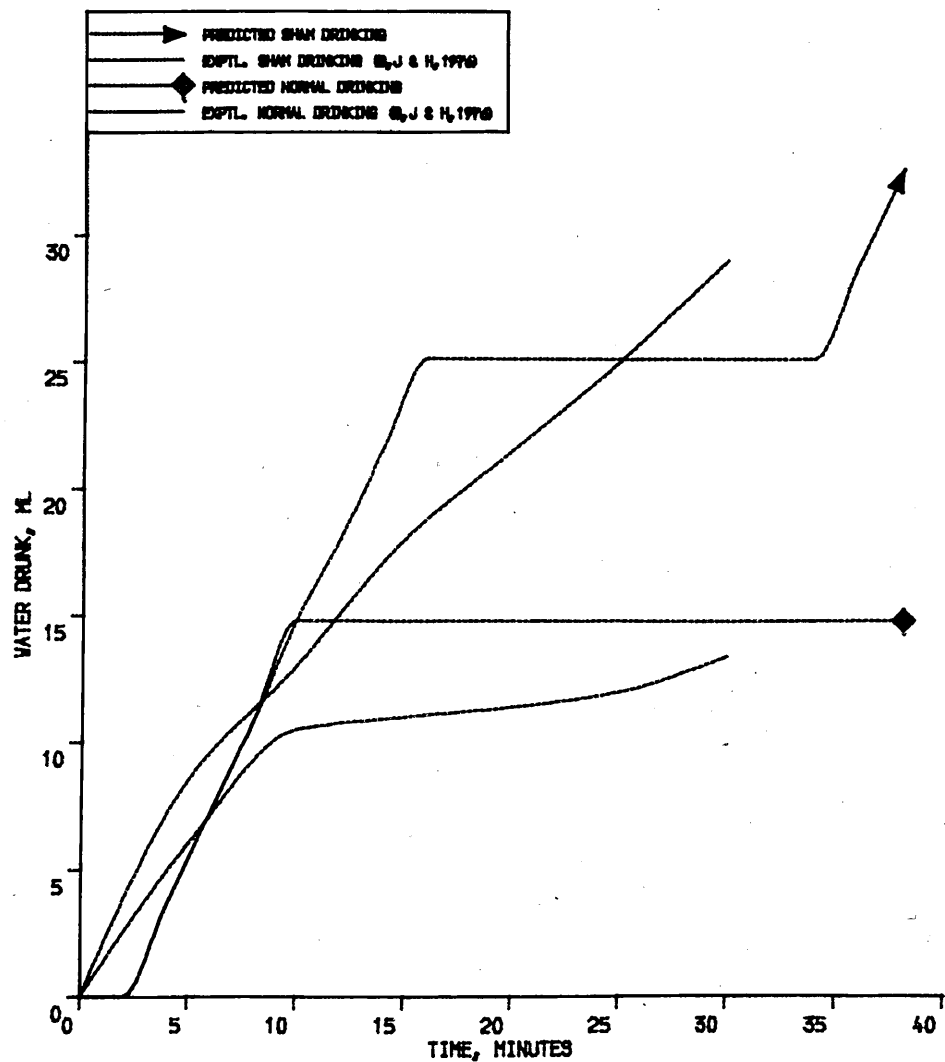
There has been considerable debate over the role played by oropharyngeal stimuli in the control of drinking in the rat. Cannon (1918) argued that although the amount drunk may be related to bodily requirements, the sensation of thirst originates in the dry mouth, and drinking is in response to the sensation that arises. On the other hand, others maintained that drinking was determined simply by the animal's hydrational state, there being no need for an oropharyngeal mediator. Thus Bernard (1857) showed that thirst could be relieved by simple infusion, by-passing the oro-pharyngeal tract altogether. This appeared to clinch the argument in favour of the hydrational theory. However, Bellows (1939) suggested that, at least in dogs, sham drinking is related to both hydrational demands and possibly stomach distension. The term 'possibly' is used with respect to stomach distension, because it is assumed that the degree of stomach distension that occurs during sham drinking would be related to the type of surgical preparation. If the ingested fluid were to flow directly out of the stomach, then there could be no distension. However, this does imply an interaction between two potential sources of fluid intake control; hydrational and oro-gastric. In addition, it appears that in fast-drinking animals (e.g. dog) sham drinking is very similar to normal drinking. When such animals sham drink, they rapidly and accurately drink sufficient water to replenish the imposed deficit. Because normal drinking in fast-drinking animals stops before the

ingested water is absorbed into the cardiovascular compartment, the hypothesis of oropharyngeal metering has developed (Adolph, 1950).

Hatton and Bennett (1970) have suggested that drinking termination in rats is primarily controlled by changes in plasma osmolality following absorption.

Blass, Jobaris and Hall (1976) considered whether these divergent findings in fast- and slow-drinking animals reflected qualitatively different drinking mechanisms, or whether the differences were only a matter of degree. The simulation described here aims to analyse the results of their study, and demonstrate the potential of even such a simple system as that used in the 'small rat'.

Blass et al (1976) water-deprived rats fitted with gastric cannulae for 12, 24 or 48 hours. The animals were then provided with water, and their drinking behaviour studied for two hours. The control animals had cannulae fitted, as did the experimental animals, but in the control animals the cannulae were blanked off. The simulation's sham drinking and normal responses to 24 hour water deprivation are shown in Figure 3.10. Experimentally-derived results are also given, for comparison. It can be seen that there is a close association between the predicted and actual results. At the end of the 2 hour test period, control animals had drunk about 13 ml water, and experimental animals 51 ml. Values predicted by the simulation were 14.4 and 54.0 ml respectively. The experimental ratio of sham to normal drinking was 4.07 to 1; the predicted ratio was 3.75 to 1. However, Blass et al



SHAM & NORMAL DRINKING AFTER 24HR WATER DEP.

FIGURE 3.10

(1976) found this ratio to be constant over all periods of water deprivation. This was not as predicted by the simulation. Although the same tendency for sham-drinking rats to drink more than their normal counterparts is still present, the ratios in both 12- and 48-hour deprived animals are less than that observed experimentally.

Nevertheless, as discussed by Blass et al (1976), this shows that the simulation, as does the actual animal, demonstrates the following behaviour;

- a) The water volume drunk by sham-drinking rats is directly related to the extent of water deprivation.
- b) Sham drinking terminates, even though none of the ingested water is absorbed.

Blass et al (1976) conclude that the differences in drinking controllers between fast- and slow-drinking animals are predominantly ones of degree. It is considered probable that the drinking system developed for use in this simulation is a realistic representation of that which operates in the actual animal.

The Effect of Gastric Preloads on Sham Drinking

Blass et al (1976) (Experiment 3) administered gastric preloads of water to sham-drinking 24hr deprived rats at the start of the 23rd hour of deprivation. At the beginning of the 24th hour (by which time the infused preload would have been absorbed), sham drinking behaviour was studied for the customary 2 hour period, as in the previous experiment. These authors found that this treatment reduced sham drinking from an average of 51 ml to 21 ml. Similar, but not so dramatic, results were obtained from the simulation. In this case, drinking reduced from 54 ml to 36 ml. Largely out of interest, the simulation was also conducted on normal animals. Here, around 14.4 ml is usually drunk following 24 hour water deprivation; the 5 ml preload (conditions as above) reduced this to about 7 ml. This represents another situation in which sham drinking of rats parallels that of the more rapid drinkers (Towbin, 1949). Thus it is possible that the mechanism simulated here to investigate rat drinking could easily be generalised to other animals. Perhaps all that need be amended for each animal are the relative weightings given to hydrational and oro-pharyngeal indices of drinking.

The Drinking Response to Infusions of Hypertonic Saline

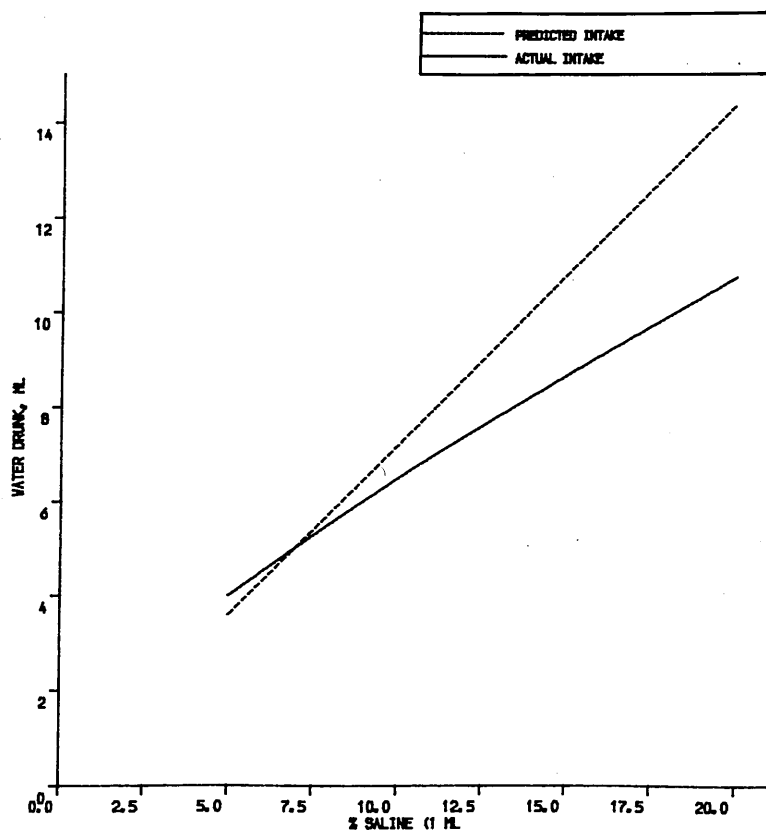
The data from this simulation are to be compared with the experimental findings of Corbit (1965). The aim of the simulation is to assess the realism of the drinking responses following 1 ml injections of water (control), isotonic (0.9%), 5%, 10% and 20% hypertonic saline. The results (experimental and predicted) are shown in Figure 3.11.

It is clear that

(a) drinking in the rat is a linear function of the amount of NaCl injected. This offers yet another instance in which the responses of a slow-drinking animal parallel that of a fast-drinking animal (dog- Di Salvo, 1955).

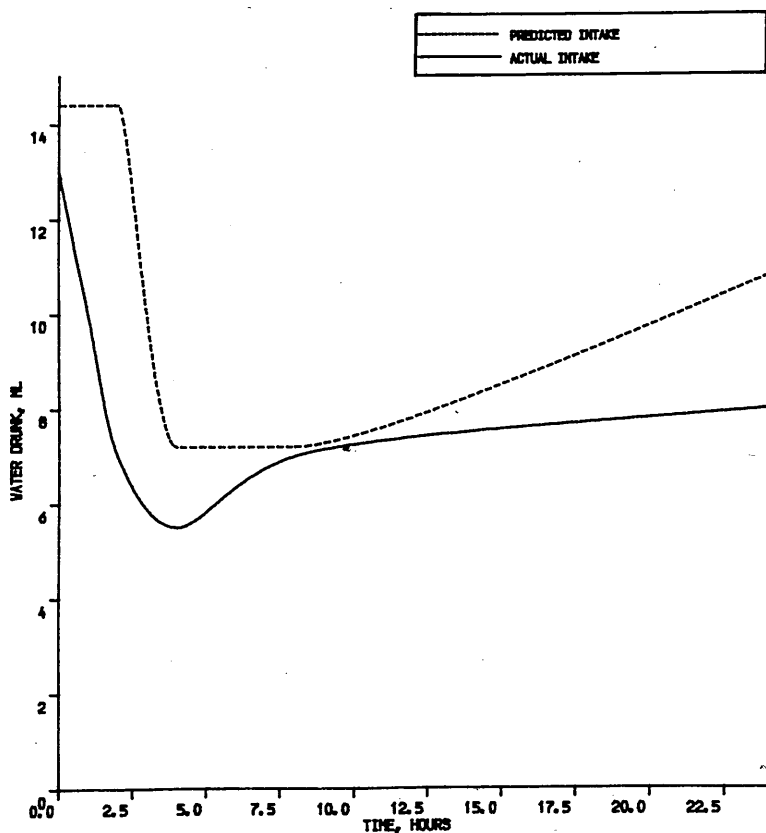
b) The model described here responds accurately to both hydrational and oro-pharyngeal drinking factors. This extends the domain of the system's realism.

It is interesting to note also that in the experiment total water ingested per gram of injected salt decreased as the concentration of the infusate increased. This was not predicted by the simulation, although both failed to drink enough to dilute the Sodium load to isotonicity. This is due to the renal system excreting some of the load, and hence reducing the water intake necessary to restore normal circumstances. The reasons for this are uncertain, and could usefully be the subject of further simulations and experimentation.



EFFECT OF HYPERTONIC SALINE ON DRINKING

FIGURES 3.11 & 3.12  
EXPERIMENTAL DATA FROM CORBIT  
(1965)



EFFECT OF DELAY AFTER HYPERTONIC SALINE

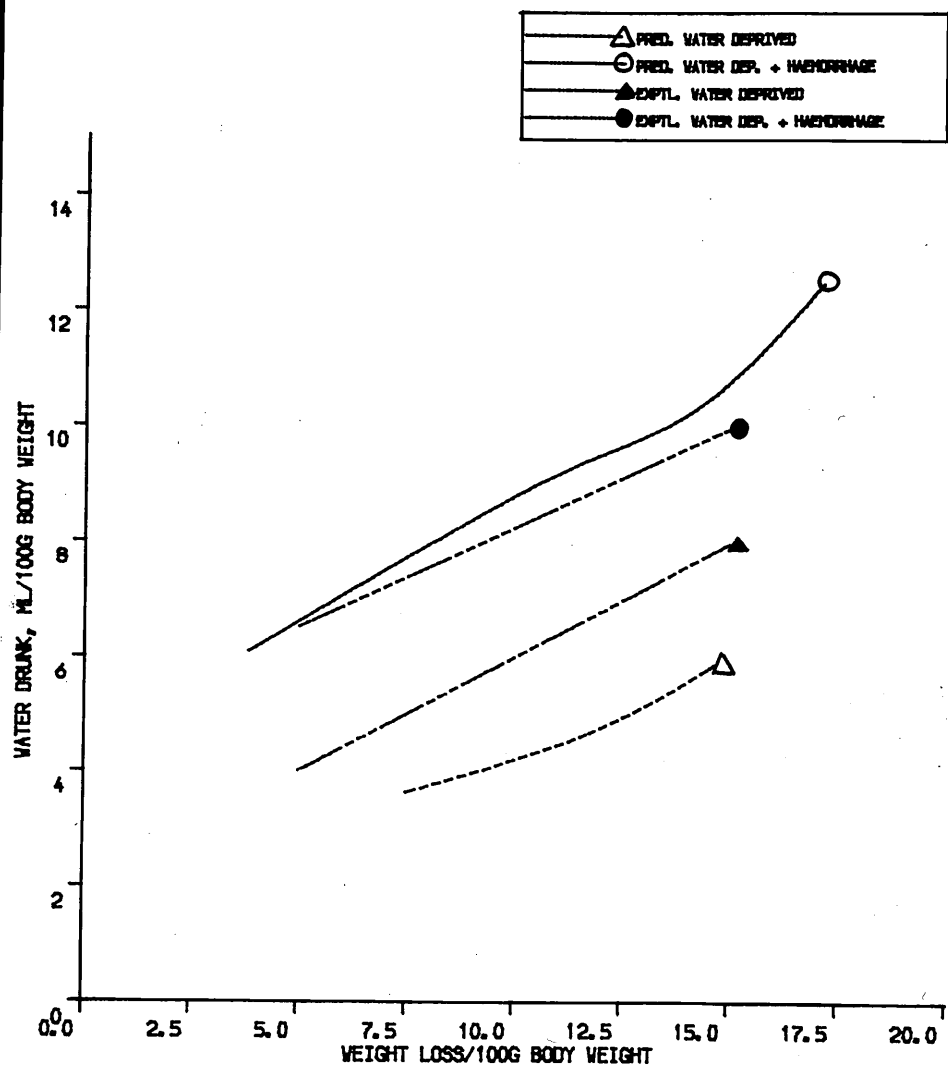
Corbit (1965) also studied the effect of imposing a delay between administration of 1 ml 20% saline and the provision of drinking water. Both the experimental and predicted results are shown in Figure 3.12. Whilst there are obvious discrepancies, it is apparent that the same trends are present in both simulated and experimental animals.



Effects of Combined Thirst Stimuli

Oatley (1964) found that in the rat the combination of haemorrhage (an extracellular stimulus to drinking) and hypertonic saline (a cellular stimulus) caused more drinking than either stimulus alone. In order to study the nature of this interaction, Fitzsimons and Oatley (1968) deprived rats of water (but not food). At the end of the deprivation period, half were simply allowed access to water, whilst the remainder received a haemorrhage, of about 5 ml. As in Oatley (1964), it was found that the combined stimulus produced more drinking than water deprivation alone (See Figure 3.13). Note that the experimental data are represented only by the regressions. The correlation coefficient of the water-deprived rat data is 0.68; that for the water-deprived and haemorrhaged rats is 0.54. Of greatest significance in this experiment is that the regressions do not differ significantly in slope, but are significantly displaced from one another, indicating that the combined effects are additive. The results predicted by the 'small rat' simulation are also shown in Figure 3.13. It can be seen that they are good fits to the experimental data. This simulation acts as a good general test of the system, as the resultant predictions are contributed to, to a greater or lesser extent, by virtually every component of the model. It does appear however that the proportionate contributions to drinking of dehydration and haemorrhage are not quite right.

It may be that the intracellular stimulus does not have adequate 'weighting' in the drinking decision system (see



EFFECT OF WATER DEPRIVATION AND HAEMORRHAGE

FIGURE 3.13  
EXPERIMENTAL DATA FROM OATLEY  
(1964)

Chapter 2). On the other hand, it is possible that haemorrhage is a bit too effective a stimulus; certainly, the additional drinking that is stimulated by the haemorrhage exceeds the volume of the haemorrhage given (5 ml). Nevertheless, the findings are encouraging.

SECTION 4 - LARGE RAT SIMULATIONIntroduction

As suggested in the introductory chapters, the simulation presented here is a complex one. Essentially, there are three body fluid compartments; the vascular, interstitial and intracellular. The mix of water, Sodium, and Potassium ions unique to each compartment is regulated by a multitude of control systems, both hormonal and neural. Each compartment is inextricably inter-related to the behaviour of all the other compartments. The control systems interact in a similarly complex way. Given this, it is difficult to consider a linear means of presentation, necessary in a textual presentation, that can place adequate emphasis on the true method by which the system operates.

Throughout, the aim has been to try and describe each portion of the system in such a way as to emphasise the manner of its interactions with all the other systems. However, this cannot have been entirely successful, and thus perhaps it would be timely to remind the reader of the integrated nature of this model. It is not easy, or even possible, to deduce the response of the entire system to a physiological intervention merely by examining the description of an individual system. To understand the total system's responses, it is normally necessary to resort to the computer representation of this model.

For similar reasons, it is also difficult to derive a rational order in which to present the individual sub-systems comprising the model. Here, it was considered most

appropriate to explain the metabolism of the body compartments first. These are the central components of the whole system, the regulation of which are the 'raisons d'etre' of all other systems. Thus Chapters 4, 5 and 6 describe the vascular, interstitial and intracellular compartments, respectively.

The following Chapters (7 to 9) describe the various systems subserving input and output of food, water and electrolytes. This includes the gastro-intestinal tract, insensible water loss system and the renal sub-system. This also includes the related systems determining food intake and energy metabolism.

The remaining Chapters in this section are devoted to the description of what may collectively be regarded as the 'control systems'. These regulate the output systems described in earlier chapters, and also contribute to the maintenance of adequate tissue perfusion pressures in the cardiovascular compartment.

Thus Chapter 10 details the renin-angiotensin system, and Chapter 11 the aldosterone system. The control of anti-diuretic hormone is described in Chapter 12, and the final Chapter (13) of this section describes the autonomic nervous system.

System DescriptionWater and Ion Flows in the Vascular CompartmentIntroduction

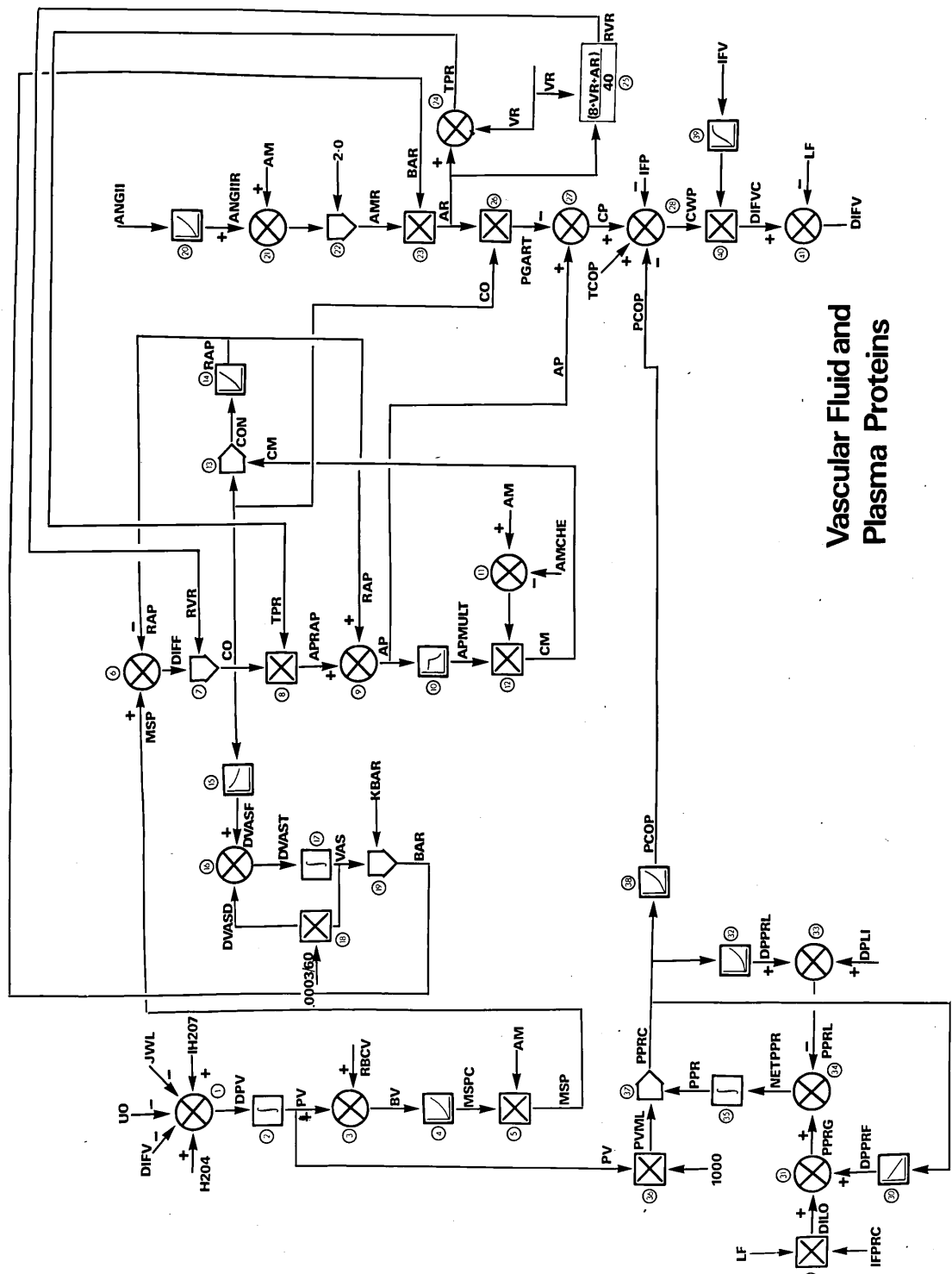
Of the three body fluid compartments, the vascular compartment is by far the most complex, due to the large number of factors that serve to maintain equilibrium. These factors are both short-term, as with autonomic activity, and long-term. Examples of the latter are renal dynamics and the degree of body vascularization. Hormonal mediators of vascular equilibrium (e.g. anti-diuretic hormone, the renin-angiotensin system and aldosterone) act as medium-term regulators.

Vascular CompartmentVascular Fluid Dynamics

As with the 'small rat' simulation, much of the system presented here is adapted from the human simulation work of Guyton and his colleagues (e.g. Guyton and Coleman, 1967; Guyton, Coleman and Granger, 1972). The basic rat cardiovascular system is the same in concept to Guyton's human system, but obviously it has been necessary in many cases to alter the functions, to cater for the vastly differing values of blood volume, resistances to flow, etc. The nature and extent of these alterations is pointed out in the course of the system description.

The general principles underlying water flows between the interstitial and vascular compartments are the same in all mammals. Starling (1896) first suggested the concept of the 'capillary equilibrium', whereby the flow of fluid across the capillary walls is determined by the dynamic balance of a number of hydrostatic and oncotic (i.e. exerted by plasma proteins) pressures (for a full description, see Guyton, 1976). This principle has been employed in both the model presented by Guyton and Coleman (1967), and that presented here.

The flow of fluid across the capillary wall, determined by the 'Starling capillary equilibrium' (Starling, 1896), is shown in Block 1, Figure 4.1. Starling pointed out that under normal conditions, a state of near-equilibrium exists across the capillary walls, whereby the net amount of fluid entering the interstitial compartment is equal to that leaving it, via lymph flow. This near-equilibrium is



Vascular Fluid and Plasma Proteins

FIGURE 4.1



produced by the sum of the mean forces tending to move fluid through the capillary membranes.\* Forces tending to move fluid out of the vascular compartment are capillary pressure, the negative value of interstitial fluid pressure, and interstitial fluid colloid osmotic pressure. Against this is plasma colloid osmotic pressure, and interstitial fluid pressure, on the rare occasions when it is positive.

Block 1 calculates the net rate of change in plasma volume in the current iteration (DPV). In most sections of this simulation the iteration interval represents one second of real time. This represents summed water flows from the stomach, intestine and interstitial compartment, as well as renal and insensible losses. Block 2 integrates this signal, to give plasma volume (PV). Wang (1959) quotes a plasma volume in rats of 40.4 ml/Kg body weight. This gives a plasma volume of about 13 ml in a 300 g rat, and is the initialisation value used here. Block 3 derives blood volume (BV) by adding red blood cell volume (RBCV) to plasma volume. Wang (1959) also found (*Rattus Norvegicus*) normal red blood cell volume to be 23.7 ml/Kg body weight, with a venous haematocrit of 50.3 per cent. Summing plasma and red blood cell volumes yields a total blood volume of 64.1 ml/Kg body weight, or about 20 ml for a 300 g rat.

Block 4 shows the relationship between blood volume and normal mean systemic pressure (MSPC), before the influence of autonomic activity is brought to bear. This may be regarded as the degree of filling of the systemic

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\* Note that as is discussed later, net flow is not the same as total flow.

circulation. Since most of the blood of the circulatory system is in the systemic circulation, whenever the blood volume increases, so also does the filling of the systemic circulation. Experimentally, mean systemic pressure can be measured by stopping the circulation and bringing the pressures in the arterial and venous areas of the systemic circulation into equilibrium. The remaining pressure is then equal to mean systemic pressure. The relationship used here is derived from published data on dogs (Richardson, Stallings and Guyton, 1961; Harlan, Smith and Richardson, 1967). For want of relevant information, it is assumed that the same normal mean systemic pressure (around 7 mmHg) pertains in both dogs and rats. In addition, the change in mean systemic pressure is assumed to be the same for proportionately equal variations in both dog and rat blood volume. Within physiological limits, the function is linear.

Sympathetic stimulation shifts the relationship between blood volume and mean systemic pressure (MSPC), by altering the compliance of the systemic circulation. This effect is represented in block 5, and is the same as that employed by Guyton and Coleman (1967) in their simulation of human cardiovascular dynamics. The effect of autonomic activity (AM) on 'normal' mean systemic pressure (MSPC) is to produce 'final' mean systemic pressure, MSP.

Block 6 subtracts right atrial pressure (RAP) from the previously derived mean systemic pressure (MSP), to give the pressure gradient for venous return (DIFF). Guyton (1955) demonstrated that blood flow into the heart is almost linearly related to this pressure gradient, at least in

dogs. It is assumed that the same also occurs in the rat.

Fluid systems are such that all pressure gradients tend to produce a flow, and as with Ohm's law, the magnitude of that flow depends on the resistance offered. Thus block 7 divides the pressure gradient (DIFF) by the resistance to venous return (RVR), to give blood flow rate into the heart. Moreover, except in the very short term (a matter of seconds), venous return is the same as cardiac output (CO).

Block 8 calculates the pressure gradient between the arteries (APRAP) and the right atrium by multiplying cardiac output and total peripheral resistance (TPR). Block 9 adds right atrial pressure to this pressure gradient, to give arterial pressure (AP).

Arterial pressure, acting as a 'back-pressure', affects cardiac function approximately as shown in block 10. Whilst arterial pressure remains below about 150 mmHg, cardiac function is unimpeded. However, as arterial pressure rises above this, the pumping ability of the heart begins to fade and actually reaches zero at about 300 mmHg. The output of this block is expressed in terms of fraction of normal. The relationship used here is derived from Guyton and Coleman (1967). The upper limit at which the heart begins to fail is increased slightly, due to the somewhat greater normal arterial pressure of rats compared to the animals studied by Guyton (dogs).

Blocks 11 and 12 represent the effect of autonomic activity (AM) on the heart. Although evidence regarding the true role of chemoreceptors in rats is not available, it appears that at least in cats chemoreceptors do not have any

effect on heart activity. Downing and Siegel (1963) showed that chemoreceptor discharge (cats) causes vasoconstriction, as do decreases in baroreceptor firing rates. It does not however cause an increase in cardiac sympathetic impulses. These authors further argue that, on the occasions tachycardia has been observed following chemoreceptor stimulation, it is a secondary response caused by the stimulation of respiration (Comroe, 1939; Heymans and Neil, 1958). Consequently, block 11 subtracts chemoreceptor influence (AMCHE) from the autonomic multiplier. Block 12 applies this to heart activity.

Blocks 13 and 14 derive right atrial pressure. Block 14 represents a Starling curve of the heart, as first published by Patterson and Starling (1914) following their experiments on dogs. This shows that as cardiac output rises, the increased volume that the heart is required to pump causes a progressively increasing back pressure in the right atrium. Block 13 feeds autonomic activity (as amended by blocks 11 and 12) into block 14 in such a way that a change in pressure load on the heart will shift the operating point in the proper direction.

Long-term deviations of cardiac output from normal induce compensatory changes in the body's degree of vascularisation. Thus a significant decrease in cardiac output (of about 20 per cent) over a period of several days will induce the growth of new capillaries, reducing peripheral resistance to blood flow, and restoring an adequate cardiac output. This system is described by blocks 15 to 19. It is designed so that at normal levels of cardiac

output (see below), the degree of body vascularisation remains constant. Block 15 relates average cardiac output to the rate of vascularity formation (DVASF). Block 16 sums vascularity formation and destruction rates to give the net formation rate (DVA<sup>ST</sup>); block 17 then integrates this to give total body vascularity at any one time (VAS), expressed as a fraction of normal. Block 18 calculates the rate of vascularity destruction (DVASD), as a function of total vascularity.

The rates of formation and destruction are tentatively derived from data provided by Patz (1965- infant human) and Schmidt-Nielsen and Pennycuik (1961- rats). Following occlusion of an artery, (e.g. Freis, 1960), blood flow to the tissues concerned becomes deficient. However, over a period of days, smaller collateral arteries gradually dilate and also sprout new branches. Eventually this can proceed to the extent that a more or less adequate supply of blood is restored to the previously deprived tissues. If blood flow through the blocked artery is restored, these newly-developed collaterals recede once more. The availability of Oxygen appears to be the major determinant of growth or recession of these collaterals (Schmidt-Nielsen and Pennycuik, 1961).

The time taken for collaterals to develop is difficult to specify exactly, but it is clear from the above discussion that significant effects on resistance to blood flow can occur in a matter of days. Such a time-scale is also indicated by Patz (1965) in his study of retinal blood vessel growth in differing Oxygen concentrations. At high

Oxygen concentrations, the retinal blood vessels of premature infants can grow so rapidly as to damage the retina and cause permanent blindness- retrolental fibroplasia. It has been assumed that the development of collaterals in the rat occurs on approximately the same time-scale as the studies cited above, which were conducted on dogs and humans.

Finally, block 19 derives basal arterial resistance (BAR), as a function of the degree of body vascularity (VAS). Vascularity is expressed as a fraction of normal (1.0), thus it needs to be converted to the appropriate normal value of basal arterial resistance. This is achieved in block 19 by the constant KBAR. This constant represents the value of arterial resistance that would permit an arterial pressure of about 120 mmHg with a cardiac output of about 1.4 ml/s. The value was derived empirically, by using the flow analogy with Ohm's law. Basal arterial resistance refers to the 'underlying' resistance presented by the arteries and arterioles, before the exertion of any short-term effects by autonomic activity or circulating angiotensin II levels. The total resistance (arterial plus venous) to blood flow can be derived from arterial pressure and cardiac output, by analogy with Ohm's law. Extrapolating from human data (Guyton and Coleman, 1967), it seems that arterial resistance comprises 83 per cent of total resistance; for want of more appropriate data, this is the value used here.

Short-term variations in arterial resistance to blood flow are mediated by autonomic activity and plasma

angiotensin II concentration. Both these exert their effects by causing a constriction of the pre-capillary arterioles. It is assumed here, for want of adequate information, that each influence has an equal effect under normal circumstances.

Block 20 converts plasma angiotensin II (ANGII) concentration to its contribution to arterial resistance. The function shown in block 20, illustrating the influence of angiotensin on arterial resistance, is somewhat speculative. To date, no information has come to light that would permit a more accurate representation, either in the rat or any other animal. At a normal plasma angiotensin concentration of about 3 pg/ml, the contribution to arterial resistance is 1, i.e. no change. Block 21 adds the contribution of autonomic activity. This, too, is normally equal to 1. Block 22 calculates the mean of these two signals (ANGIIR and AM); this is the form in which it is used, as a fraction of normal (1). Block 23 derives arterial resistance (AR) by combining basal arterial resistance and the short-term influences discussed above.

Not all the resistance to blood flow occurs in the arteries; the venous system also exerts a resistance, albeit less than the arterial system. Thus block 24 sums arterial and venous resistances, to give total peripheral resistance.

Arterial and venous resistances also contribute to the resistance to venous return (RVR), calculated in block 25. The resistance to venous return is equal to the average resistance from each portion of the systemic circulation to the right atrium, when each portion is weighted according to

the compliance of that portion. Venous compliance is much greater than arterial, thus the resistance of the veins plays a more significant role in determining venous return than does arterial resistance. The result of this block is fed back to block 7, for the calculation of cardiac output. The function used in block 25 is the same as that used by Guyton and Coleman (1967), in their simulation of the human cardiovascular system. It is assumed that the weightings given, to represent venous and arterial compliances, remain as before.

By analogy with Ohm's law, block 26 calculates the pressure gradient in the arteries, by multiplying cardiac output and arterial resistance. This, when subtracted from arterial pressure in block 27, gives mean capillary pressure. This is employed in block 28 as a determinant of net hydrostatic pressure across the capillary wall, otherwise referred to as Starling's capillary equilibrium (see earlier in this section).

The determination of a 'normal' cardiac output is not easy, as it can be significantly affected by a wide range of factors. Jansky and Hart (1968) show that rat cardiac output varies with the degree of acclimatisation, and ambient temperature. Of all conditions given, however, that of a warm-acclimatised rat in normal conditions is probably closest to those experienced by a laboratory animal. The average cardiac output for such animals is 290 ml/minute/Kg body weight. Popovic and Kent (1964) report a similar value of 286 ml/minute/Kg b.w. in the conscious adult male *Rattus Norvegicus*. The corresponding value for anaesthetised animals



is somewhat lower, at 204 ml/minute/Kg b.w., serving to emphasise the danger of using data from anaesthetised animals. An unexpected difficulty may be indicated by Wostmann et al (1968), who reported that the cardiac output of germ-free Wistar rats is only some 70 per cent of that observed in normal Wistars. However, from the figures given above a normal value of cardiac output for a 300 g rat would be about 1.4 ml/s. This is the value used in the current simulation.

The subject of rat arterial pressure is briefly reviewed by Altman and Dittmer (1971). Of the 21 reports cited, 15 give an average systolic pressure of between 100 and 130 mmHg. Individual variations are, in all cases, great. Diastolic pressures unfortunately receive somewhat less attention, but it was felt that an average arterial pressure of about 110 mmHg could be regarded as normal.

Capillary pressure in rats has been studied by a number of authors, using a variety of techniques. Values for arteriolar capillary pressures vary between 24 cm H<sub>2</sub>O, using capillary tonometry (Algive, 1953), and 31 cm H<sub>2</sub>O, using direct cannulation (Smaje et al, 1970; Wind, 1937). In each case, venous pressures are around 17 cm H<sub>2</sub>O. The mean capillary pressure should thus be around 25 cm H<sub>2</sub>O. This is the basis for the value used in this simulation. Note that the units used here are mm Hg. Thus the above figures should be divided by a conversion factor of 1.32.

Blocks 29 to 38 are responsible for the maintenance of plasma protein, and the colloid osmotic pressure arising therefrom. There is a gradual turnover of plasma proteins,

and under normal circumstances the gain of plasma protein by the cardiovascular system is equal to the rate of loss. Plasma protein concentration remains fairly constant under normal circumstances, at least in adult life. Apparently this is not the case in young (pre-pubescent) rats (Metcoff and Favour, 1944), but the model presented here is of a mature animal.

The half-life of plasma albumins (which are responsible for most of the colloid osmotic pressure exerted by the plasma) is about 10 days, at least in humans (Beeken, Volwiler et al, 1962). The same figures are assumed to be pertinent to the rat, and are therefore used to derive the constants determining plasma protein turnover. The subject of plasma protein metabolism is reviewed by McFarlane (1964). He presents evidence that the normal sites of both protein destruction and formation are closely allied with the vascular (rather than the interstitial) compartment. Thus in the model presented here, all plasma protein formation and destruction occurs in the vascular compartment. This has the additional advantage of simplifying the system somewhat.

Block 29 calculates the flow rate of plasma protein from the interstitial compartment, via lymph flow (DPLO). Block 30 calculates the rate of plasma protein formation (DPPRF), as a function of plasma protein concentration. Block 31 then sums these two gain rates to give total gain (PPRG).

Block 33 sums protein losses from the plasma (PPRL), due to its natural breakdown (DPPRL- calculated in block 32)

and the slight flow across the capillary walls into the interstitial fluid compartment (DPLI). Block 34 calculates net rate of plasma protein gain or loss (NETPPR), and block 35 integrates this signal to give total plasma protein (PPR). This, divided by an appropriately converted value of plasma volume, gives plasma protein concentration (PPRC-blocks 36 and 37).

Plasma protein concentration has been related to a number of physiological states. Allison (1950;1953) showed that the nutritional state of an animal can influence turnover of plasma proteins, and thus the colloid osmotic pressure exerted. Allison's studies were conducted on the dog, but his results have been largely confirmed by the rat studies of Brazzuna, Pierce and Libermann (1975) and Libermann, Brazzuna et al (1976). Prolonged protein deprivation in each case eventually reduces the plasma protein concentration. In the medium term however, the proportional plasma water depletion is greater than the loss of plasma protein. Thus over a period of up to 15 days of water deprivation, plasma protein concentration will first rise, then start falling around day six (Libermann, Brazzuna et al, 1976). Such decreases in osmotic pressure are often responsible for starvation-induced oedema, in which the Starling capillary forces withdraw fluid from the vasculature into the interstitial spaces.

Many other, more acute, physiological interventions can temporarily disturb the balance of plasma protein synthesis and catabolism. Stewart and Rourke (1936) and Guyton, Lindley et al (1950) showed that, following haemorrhage,

plasma protein concentration falls, presumably due to a 'dilution' of plasma by interstitial fluid.

Block 38 calculates plasma colloid osmotic pressure as a function of plasma protein concentration. The relationship used here is derived from Ott (1956- humans), being the best fit available to the experimental data relating whole-blood plasma protein concentration (as opposed to any individual components) to colloid osmotic pressure.

The colloid osmotic pressure of rat plasma has been reported by Keys and Hill (1934) at around 20 mmHg. This is somewhat less than the average human value of 27 mmHg. Using this, and the data provided by Ott (1956), a normal plasma protein concentration of 0.06 mg/microl can be derived. This is the value used in the current simulation.

Blocks 39 to 41 determine the net rate of plasma water gain or loss (DIFV). Fluid can always flow freely from the cardiovascular to interstitial compartments when driven by a positive capillary wall pressure. However, the same is probably not true of fluid flow from the interstitial compartment. Under normal circumstances, the largest part of interstitial fluid is in fact a gel, mostly hyaluronic acid (Guyton 1976, p.407). Thus as interstitial volume falls, the amount of free fluid available is rapidly depleted. There is, unfortunately, little direct evidence to support this notion. Koven, Gallie et al (1972) have shown that following haemorrhage (in the rat), substances could not diffuse as easily through the interstitial spaces as they could under normal circumstances. This may well be due to the shortage of free fluid, unbound to the interstitial

gel. It is interesting to note that this slowing down of diffusion rates may contribute to cellular injury following shock, due to the inadequate transport of nutrients. The shortage of interstitial fluid has the effect of reducing the trans-capillary ultrafiltration coefficient. Thus block 39 reduces the filtration coefficient whenever capillary wall pressure is negative, and interstitial fluid volume is depleted. Block 40 applies the filtration coefficient to mean capillary wall pressure (CWP), giving the net flow rate across the capillary walls (DIFVC). Block 41 subtracts lymph flow from this trans-capillary flow rate, to give the net gain or loss of fluid to the plasma (DIFV).

It is important to note that this net flow is very much less than the total fluid flow (Guyton, 1976, p.388). Thus substances capable of freely diffusing across the capillary walls will rapidly reach an equilibrium within the vascular and interstitial compartments. Hevesy and Jacobsen (1940) showed that injections of heavy water into the rabbit were equally distributed between the vascular and interstitial spaces within only about half a minute. (The analogous interaction between cellular and extracellular water took about half an hour). Similarly, Flexner, Gellhorn and Merrell (1942) found that, in the Guinea pig, 73 per cent of the blood water is exchanged with interstitial fluid every minute. In all cases, the net flow of fluid was minimal; there was simply a 'one-for-one' exchange. The responses to an actual imbalance, as would occur in haemorrhage, are very much slower (e.g. Chien, 1958; Oberg, 1963). This is because the flows induced are a consequence of hydrostatic and

osmotic pressure gradients.

### Validation of the Cardiovascular System

Unfortunately, apart from data on normal performance, there is not a great deal of independent data available on the rat cardiovascular system. To an extent, one can argue that the fact it works at all, and that equilibrium values match published data on arterial pressure and cardiac output is some validation. Thus the predicted value of arterial pressure under normal circumstances varies between 110 and 120 mmHg, whilst cardiac output is between 1.4 and 1.5 ml/s. To compare with experimental data, see references earlier in this section. In addition, because of its central nature, virtually every experiment simulated presented bears silent testimony to the accuracy of the cardiovascular subsystem described here.

However, whenever possible it is desirable to analyse the behaviour of an individual component of the overall simulation for realism. As mentioned above, this is particularly difficult for the rat cardiovascular system, due to a lack of published data. Thus a brief comparison is presented here with an experiment originally conducted on dogs.

Guyton (1976), p.270 illustrates a typical reflex change in arterial pressure caused by clamping the common carotids. This procedure reduces the carotid sinus pressure; the vasomotor centre (the activity of which is determined by the autonomic nervous system) thus becomes more active than

usual. This causes arterial pressure to rise, and to remain elevated for as long as the carotids are clamped. Removal of the clamps allows the pressure to fall immediately to slightly below normal, as a momentary over-compensation, and then to return to normal within a few minutes.

This experiment was simulated in the large rat, to test the responses of the cardiovascular and autonomic systems. It was found that the pattern of response matched exactly this description. Unfortunately, a direct comparison is pointless, as the experiments are in different animals.

Further validation of the cardiovascular subsystem presented here is given by the 'small rat' simulations of haemorrhage responses, described in Chapter 3. The cardiovascular system of the 'small rat' is identical to that of the 'large rat'.

Plasma Inorganic Ion MetabolismIntroduction

Strictly speaking the system discussed here (Fig. 4.2, in conjunction with interstitial ion dynamics) represents the distribution of available ions throughout the appropriate compartment, rather than metabolism. Ion inputs to the vascular system are determined by the behaviour of the gastro-intestinal tract (both stomach and intestine), and losses from them are determined largely by the renal system. Both input and output systems are discussed elsewhere in this volume.

However, to assume that this system merely plays a passive role in the overall model is to misunderstand the nature of its integration. Plasma ion concentration (usually referred to in terms of its total osmolality), and its homeostasis, is of vital importance to the animal. Being in such intimate contact with all other body compartments, it truly forms part of Bernard's 'milieu interieur'. Plasma osmolality is affected by most physiological interventions, such as dehydration (Brazzuna, Pierce and Libermann, 1975), starvation (Wright, Reynolds and Kenny, 1976), peritoneal dialysis, (Semple, 1952) and even just eating food (Deaux and Kakolewski, 1971). In turn, plasma osmolality is a major influence on circulatory levels of anti-diuretic hormone (Dunn, Brennan, Nelson and Robertson, 1973; Moore, 1971), aldosterone (Bull, Hillman, Cannon and Laragh, 1970) and renin (Gordon and Pawsey, 1971). Increased levels of plasma osmolality invariably act as stimuli to drinking (Hatton and Almlie, 1969), as well as





influencing all the systems mentioned above.

Thus, far from being a passive recipient of the wills of other systems, this part of the model actually forms the lynch-pin, integrating the activities of other parts.

### System Description

In Figure 4.2, the distribution of plasma ions is illustrated by blocks 1 to 20, the remaining blocks being responsible for the similar activities of the interstitial compartment. Blocks 1 to 6 represent plasma Sodium turnover. Block 1 sums gastro-intestinal (NAS6 and NAI4), interstitial (DIFNA1 and DPNA1) and urinary flows (UONA), to give the net rate of change of Sodium (DPNA). Block 2 integrates this to give total plasma Sodium (PNA), and block 3 divides this by plasma volume, yielding the plasma concentration (PCNA). Normal rat plasma Sodium concentrations are around 3.01 mg/ml, or 144 mOsmols/l (e.g. Haack, Mohring et al, 1977). In this simulation, unless stated otherwise, electrolyte concentrations are expressed as mg/ml. This is very similar to human values (Guyton, 1976). Thus the initialisation value for total plasma Sodium is normally around 40 mg.

Block 4 calculates the flow rate of Sodium into the interstitial compartment (DPNA1). At normal concentrations, this is equal to the rate of flow from the interstitial compartment into the vasculature (DIFNA1). The equilibrium plasma concentration of Sodium is slightly greater than the corresponding concentration in interstitial fluid (144 against 137 mOsmoles/l respectively- Guyton, 1976, p.432). This is due to an effect called the Donnan equilibrium. The

proteins contained in the plasma generally form negative ions, and to balance these a large number of positively charged ions (mainly Sodium) are held by the protein's electronegative charges. Proteins similar to those in plasma are also present in the interstitial fluid, but in much lower concentrations. Consequently the Donnan equilibrium is much less of an influence in the interstitial fluid, and thus Sodium ions are preferentially attracted to the plasma fluid from the interstitial fluid. In this simulation, this tendency is represented by slightly different constants determining inorganic ion flows to and from the vasculature. Incidentally, this tendency of the plasma proteins to attract positive ions in effect increases the osmotic pressure that they exert. In addition, the magnitude of the effect increases with protein concentration, producing the 'power curve' relationship observed by Ott (1956); Guyton (1976), p.393.

Blocks 5 and 6 convert the concentration of Sodium from mg/ml to mOsmoles/liter. This contributes to the calculation of total plasma osmolality in block 19. Blocks 5 and 6 could of course be incorporated into one, but they are shown as two, in order to illustrate the derivation of the constant. The value of 23 is the atomic weight of Sodium; 1000 is the conversion factor from ml to l. Thus the effective constant is  $1000/23$ .

The remaining two subsystems, representing plasma Chloride and Potassium ion metabolism, act in an identical manner to the Sodium subsystem. As may be gathered from the above discussion, the negative Chloride ions are

preferentially gathered in the interstitial compartment, a consequence of the Donnan equilibrium. The constants determining Chloride ion flow to and from the plasma are therefore the other way around, compared with the Sodium and Potassium subsystems. CLS6 and CLI5 represent the flow of Chloride ions from the stomach and intestine, respectively. DIFCL1 is the gain of Chloride from the interstitial, whereas DPCL1 is the loss of Chloride to the interstitial. The constant in block 10 is slightly greater than the corresponding constants in blocks 4 and 16; this is to reflect the greater ease with which the negative Chloride ion can cross into the interstitial compartment, relative to positive ions. KS9 and KI5 are the stomach and intestine Potassium flows; UOK represents urinary loss. DIFK1 is the gain of Potassium ions from the interstitial compartment, whilst DPK1 represents the loss of Potassium ions to the interstitial compartment. All ion flow rates are in mg/s, and thus all quantities are in mg. Nevertheless, in order to understand the principle of any plasma inorganic ion subsystem, it is only necessary to examine the appropriate section of the Sodium subsystem.

Block 19 calculates total plasma osmolality (POSM), summing the effects of Sodium, Chloride, Potassium, Calcium, Bicarbonate ions and glucose. (Only the first three are regulated in this system). Block 20 converts the total plasma osmolality derived in block 19 to plasma osmotic pressure (POP). The constant used is derived by multiplying two factors. Osmotic pressure at body temperature is approximated by osmolarity multiplied by 19.3. However, as

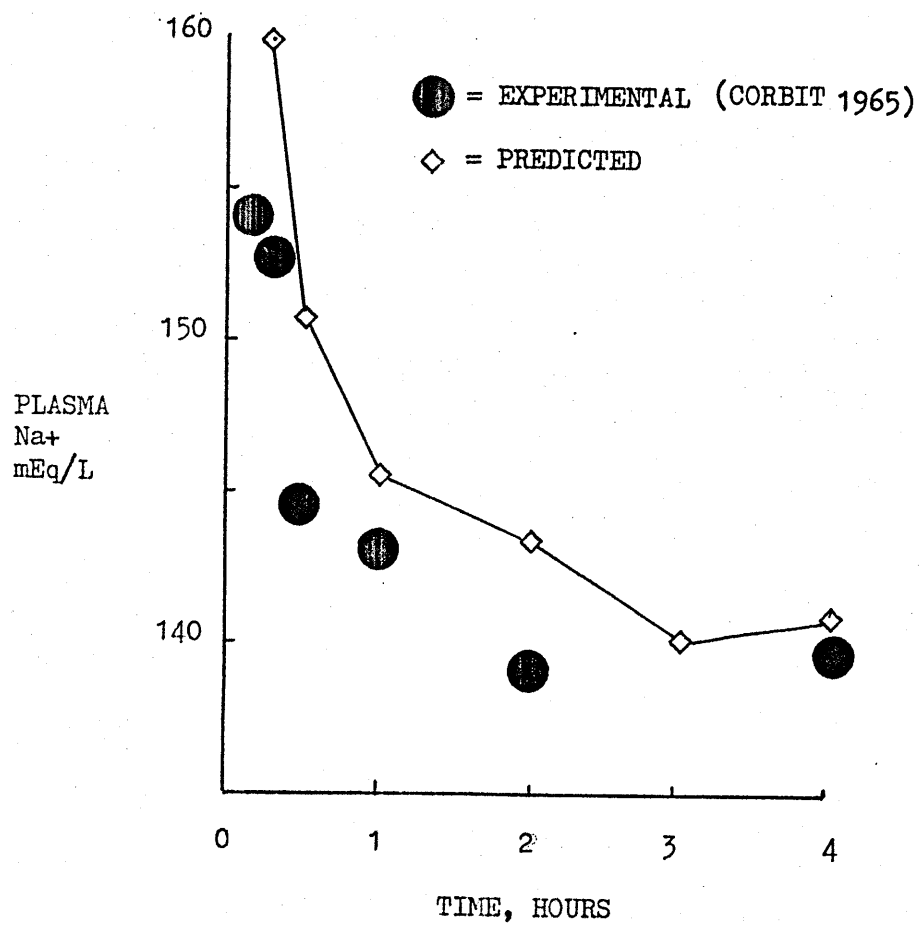


FIGURE 4.3- PLASMA SODIUM CONCENTRATIONS  
AFTER INJECTION OF 1ml 20% NaCl  
AT  $t=0$ .

the total osmotic pressure is exerted by a mixture of interacting solutes, a correcting factor needs to be applied. The value of this is 0.93 (Guyton, 1976). Due to intermolecular attractions, which tend to 'clump' otherwise free ions into aggregates, the effective osmotic pressure is less than the sum of the individual components. This is further explained by Guyton (1976).

#### Validation of the Vascular Inorganic Ion System

Corbit (1965) studied plasma Sodium concentrations following intravenous injection of 1 ml 20 per cent saline. This experiment was simulated; these two sets of results are shown in Figure 4.3. It can be seen that there is a fair agreement between the two.

CHAPTER 5Interstitial Fluid and Protein DynamicsInterstitial FluidIntroduction

The interstitial fluid lies, as its name suggests, in the spaces between the cells. A small proportion of it is in the form of freely flowing liquid, in which state it is often captured by the lymph vessels and returned to the vasculature. The greater proportion of interstitial fluid however is held in the gel of the interstitial spaces, as discussed elsewhere in this chapter (Guyton, 1976). The gel prevents all but the tiniest flow of fluid through the tissue spaces, yet dissolved substances can still pass with relative ease throughout the interstitial compartment by the process of diffusion (Guyton, 1976, p.425). Nevertheless, there is some evidence to suggest that even the rate of diffusion is dependent to some extent on the availability of free fluid (Koven, Gallie et al, 1972).

Fluid is returned to the vascular compartment via the lymph system, which acts as part of an interstitial volume-regulating mechanism. These mechanisms apply only to the small fraction of interstitial water that occurs as free fluid. Most is held as a gel, through which substances are transported by diffusion. Nevertheless, the free fluid that is held in the interstitial compartment can act as a 'reserve', helping to maintain plasma volume in times of

fluid deprivation (Koven, Gallie et al, 1972; Taylor, Gibson, Granger and Guyton, 1973).



System Description

Block 1 (see Figure 5.1) subtracts lymph flow from the rate of fluid flow across the capillary walls, to give the net loss or gain of fluid from the vascular compartment (DIFV). Fluid flows from the intracellular compartment are incorporated in block 2, and block 3 integrates this signal to give interstitial fluid volume (IFV).

Measured interstitial fluid volumes appear to vary considerably between subjects, be they humans, rats or dogs (Gauer, Henry and Behn, 1970). This may in turn cause considerable individual differences in the response to shock (Koven, Gallie, Lo and Drucker, 1972).

As with the vascular system, the interstitial compartment may be regarded as being contained in an elastic bag. In other words, the interstitial space has compliance. Until the 1960's, this problem received little attention, partly because measurements of interstitial fluid pressure were considered unreliable (Gauer, Henry and Behn, 1970). The problem was overcome by Guyton and his colleagues (e.g. Guyton, 1963), who invented the technique of implanting perforated capsules in tissues, and then measuring their internal pressure. Using this technique, it was possible to derive a relationship between interstitial fluid volume and the pressure exerted by that fluid (Guyton, 1965). This relationship is represented by block 4. This pressure is exerted throughout the compartment, but it is physiologically most effective at the boundary between the interstitial and vascular compartments, where it is a determinant of trans-capillary flow (i.e. Starling's

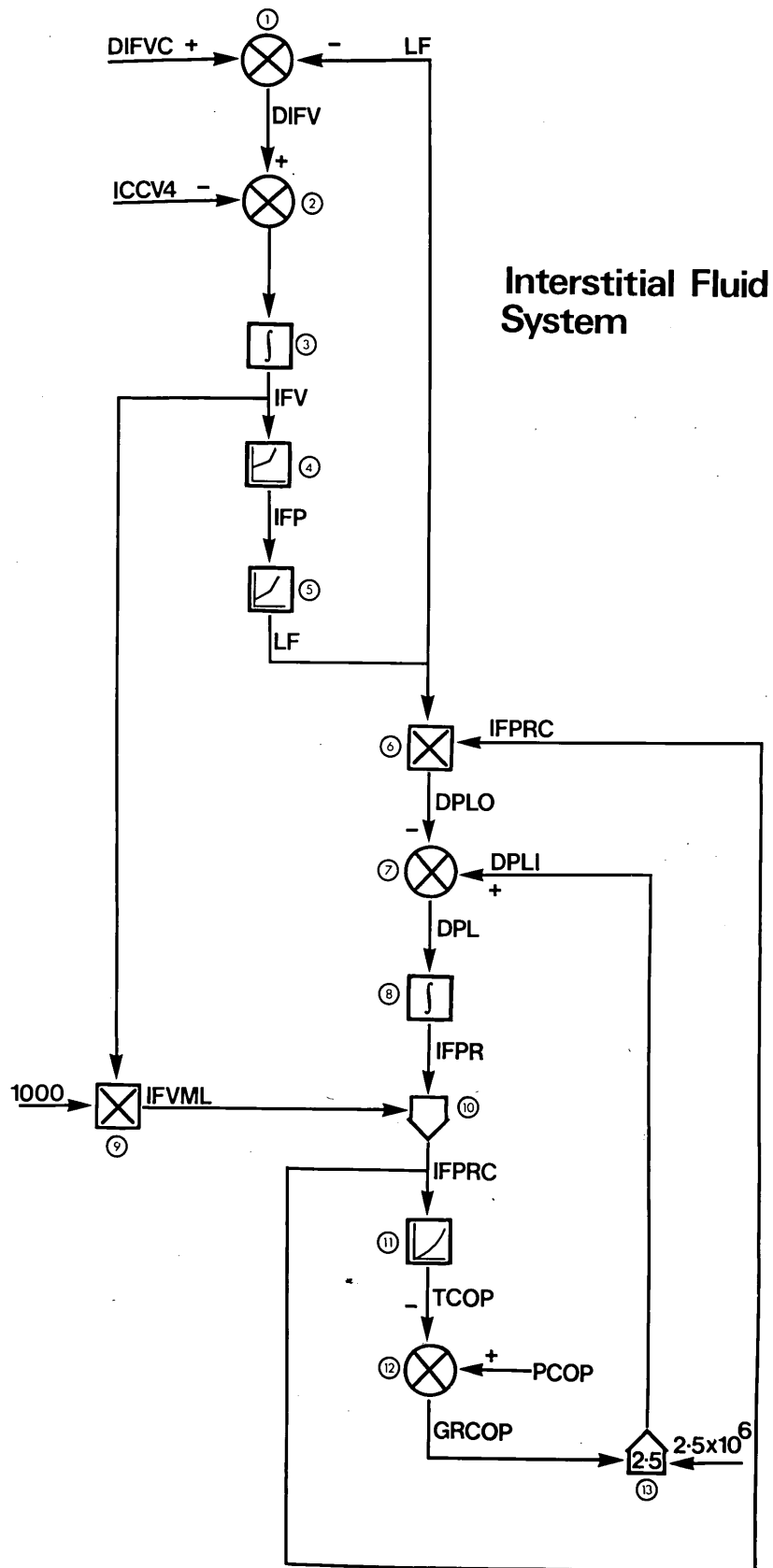


FIGURE 5.1

capillary equilibrium- see above). Somewhat paradoxically, it appears that under normal circumstances the interstitial fluid pressure is slightly negative with respect to atmospheric; a finding common to many mammals studied to date, including rats, dogs and humans. This slight negative pressure is created by a combination of the osmotic pressure exerted by plasma proteins attracting free fluid into the vasculature, and the pumping effect of lymph ducts (Gauer, Henry and Behn, 1970). Although the concept of a negative interstitial fluid pressure initially received a sceptical acceptance, it has now largely been accepted, and its role in extracellular fluid regulation thoroughly investigated (Guyton, Granger and Taylor, 1971; Taylor, Gibson, Granger and Guyton, 1973). Reliable values for rat interstitial fluid pressure of about -2 mmHg (with respect to atmospheric) have been published by Trippodo (1982). This value, which verified the indirect fluid pressure estimation using Starling's capillary equilibrium function, has been used in the current simulations. This also gives some idea of the volume/pressure (i.e. compliance) relationship.

Most 'fluid' contained in the interstitial compartment is in fact combined with protein, forming hyaluronic acid gel (Guyton, 1976, p.407). Thus normally there is very little free fluid available, and the negative pressure tends to maintain this situation. This may not significantly affect the ease with which molecules can diffuse through to the cells, at least under normal circumstances. It does however hold the interstitial fluid firmly in place. The clinical condition of oedema arises when there is excess fluid

present in the interstitial compartment; under these circumstances, fluid pressure is positive.

Lymph flow is also positively related to interstitial fluid pressure. Thus an increase in fluid pressure produces a compensatory increase in lymph flow. This relationship is given in block 5, and is derived from Taylor et al, (1973) and Trippodo, (1982). Other estimates of lymph flow, and the constitution of lymph fluid, have been published by Friedman, Byers and Omoto (1955). The area has been briefly but extensively reviewed by Altman and Dittmer (1971). They conclude that total lymph flow in a 300 g rat is about 0.7 ml/hour. This (appropriately converted to ml/s) is the value used in this simulation.

#### Interstitial Protein

The interstitial fluid proteins are generally of the same composition as plasma proteins (Ott, 1956). However, as they cannot easily cross the capillary walls, the concentrations are lower (Friedman et al, 1955). An assumption made here is that the natural 'decay' of these proteins occurs only in the vascular compartment. This simplifying assumption, which may or may not be true, does not affect in any way the performance of the model.

Block 6 multiplies the rate of lymph flow by interstitial fluid protein concentration, to give the loss rate of interstitial protein in lymph fluid (DPLO). This, when subtracted from the rate of protein flow across the capillary wall (DPLI- block 7), gives the net rate of protein flow into the interstitial compartment (DPL). Block

8 integrates the output of block 7 in the normal manner to give the total amount of plasma protein available in the interstitial fluid compartment (IFPR) capable of exerting an osmotic pressure (IFPRC). Although as mentioned earlier, the concentration of proteins in the interstitial fluid is much lower than in plasma, the correspondingly larger volume of the interstitial compartment means that under normal circumstances the actual amounts of protein in the two compartments are similar.

Blocks 9 and 10 derive interstitial fluid protein concentration, in the units appropriate (mg/microl.) for calculation of the colloid osmotic pressure exerted by these proteins, in block 11. This pressure, frequently referred to (somewhat erroneously one would have thought) as 'tissue colloid osmotic pressure' (TCOP), is another factor in Starling's capillary equilibrium, and thus helps determine trans-capillary fluid flow. The function used in block 11 has a wide range of validity, and is the same as used for derivation of vascular osmotic pressure in humans (Ott, 1956).

Compared to water, the permeability of capillary walls to plasma proteins is very low. Nevertheless, flows of protein do take place down the concentration gradient, and this is represented by blocks 12 and 13. Block 12 calculates the plasma protein colloid osmotic pressure gradient across the capillary walls; it is assumed that the slight leakage of proteins between the vascular and interstitial compartments is directly proportional to this gradient (the flow is passive). The constant in block 13 is derived

empirically. It was calculated by assuming that under normal equilibrium conditions, the trans-capillary flow of protein into the interstitial compartment will equal the loss of protein via lymph fluid (IFPRC remaining constant). Since good estimates of plasma and interstitial protein concentrations exist, as do estimates of lymph flow in the rat (see elsewhere for references), one can have some confidence in the value of this constant.

Clinical conditions that impair the function of the capillary walls, and thus increase its permeability to proteins frequently result in local or general oedema. Thus blisters occur because heat or friction has locally increased capillary permeability. Proteins are now free to flow into the interstitial spaces, and the resultant increase in interstitial fluid osmotic pressure withdraws plasma from the vasculature. Burns are a frequent cause of increased capillary permeability because overheated capillaries become friable, and their pores enlarge. A more drastic version of the same phenomenon occurs following infection with *Clostridium oedematiens* (Guyton, 1976, p.407). Here, plasma loss into the interstitial compartment kills the patient within a few hours.

#### Interstitial Fluid Ion Metabolism

As discussed earlier, most interstitial fluid is contained in a gel, consisting mainly of hyaluronic acid (Guyton 1976, p.407). Nevertheless, it fulfils an important function as a 'reserve', helping to maintain an adequate plasma volume in times of deficit (Taylor, Gibson, Granger

and Guyton, 1973). Fluid is drawn into the vasculature by an imbalance of Starling's capillary forces, aiding to restore plasma deficits, whether caused by haemorrhage (Adolph, Gerbasi and Lepore 1933; Oberg, 1963; Haddy, Scott and Molnar, 1965; Koven et al, 1970) or starvation and dehydration (Dicker, 1949).

The interstitial compartment also acts as a reserve for plasma electrolytes, storing ions in times of plasma excess and releasing them in times of deficit (Mogharabi and Haines, 1973). These responses are largely the result of a passive electrolyte flow down a concentration gradient, although any fluid transferred by pressure gradients across the capillaries will of course also carry electrolytes.

The flow of interstitial ions (Sodium, Chloride and Potassium) is represented by blocks 20 to 40, Figure 4.2. Each of the three electrolyte subsystems are identical. Consequently only one, that for Sodium, is described in detail. In order to understand the role played by each section of the other two subsystems, one should refer to the appropriate blocks in the Sodium subsystem.

The interstitial Sodium subsystem is represented in blocks 21 to 26 of Fig. 4.2. Block 21 sums losses and gains of Sodium ions from the vascular (DIFNA1, DPNA1 respectively) and intracellular (DICNA) compartments, yielding the net rate of Sodium ion flow (DIFNA). As elsewhere, ion flows are in mg/s. This is integrated in block 22 to give total interstitial Sodium (IFNA). Interstitial concentration of Sodium (IFCNA) is derived in block 23, and block 24 calculates the flow rate of Sodium

ions out of the interstitial fluid and into the plasma (DIFNA1), as a function of interstitial concentration. The constants used in blocks 24, 30 and 36 are empirically derived, considering normal interstitial ion concentrations in the rat, and the influence of the Donnan equilibrium. This topic is discussed in greater depth in the section on plasma inorganic ion metabolism. Blocks 25 and 26 convert the interstitial concentration from mg/ml to mOsmoles/liter. The output of block 26 represents the contribution of Sodium ions to total interstitial osmolality. This total osmolality is determined by block 39. This, in addition to the three 'controlled' electrolytes, also includes the influences of Calcium and bicarbonate ions, and glucose. Block 40 converts the total interstitial osmolality to an approximation of total osmotic pressure. Arguments for the constant used in block 40 are given in the section describing plasma inorganic ion metabolism.

#### Capillary Permeability From Interstitial Fluid to Plasma

As discussed elsewhere, the balance of forces present at the capillary walls can be determined by use of Starling's capillary equilibrium (Starling, 1896). The actual fluid flow that occurs as a consequence of any net imbalance of pressures is in turn determined by the permeability of the capillaries to fluid (or any solute). Provided the fluid flows from the vasculature into the interstitial compartments, the permeability coefficient remains constant (Renkin and Zaun, 1955; Oberg, 1963). Only such events as injury to the capillary membrane can



significantly affect capillary permeability, and hence the flow of fluid in this direction. (For a review of this subject, see Landis and Pappenheimer, 1963).

However, can the same capillary permeabilities be said to hold in the case of fluid flow from the interstitial to vascular compartments? This is unfortunately rather difficult to ascertain experimentally, as the technique normally used to induce hypovolemia (and hence fluid shift into the vasculature) is haemorrhage, and this has a multitude of other effects, which cloud the issue (e.g. Zweifach, Lowenstein and Chambers, 1944). Undoubtedly, interstitial fluid does help maintain an adequate blood volume. However, it is felt that the restoring capacity of the interstitial spaces is limited, because as stated elsewhere, most of the interstitial 'fluid' is in fact trapped as a gel. Thus whilst the potential for fluid transfer across the capillary boundary may well remain the same whichever the direction of flow, the actual availability of fluid capable of flowing from the interstitial compartment may be limited. Consequently, the capillary permeability in this direction is varied, according to the volume of the interstitial fluid compartment, and hence the availability of free fluid. The function used is derived from Guyton, Granger and Taylor (1971), and is shown in block 39, Figure 4.1. Unfortunately, no rat data appears to be available.

Validation of the Interstitial Fluid System

As may be gathered from the preceding discussion, there is an unfortunate lack of experimental data on the dynamics of interstitial fluid. Thus it is not possible to directly validate this system. One can, however, have some faith in it; previous simulations (see Chapter 3) have shown that the response to haemorrhage is realistic, and the individual components of the system are solidly based on published data.

CHAPTER 6Intracellular CompartmentIntroduction

Being so intimately in contact with the other body fluid compartments, it is perhaps not surprising that flows of intracellular fluid across the cell membranes occur in response to many changes in extracellular conditions. Dehydration affects cellular volume (e.g. Elkinton and Winkler, 1944; Dicker, 1949; Annegers, 1954), as does any alteration in extracellular ion concentrations (e.g. Darrow and Yannet, 1935; Mellors, Muntwyler and Mautz, 1942). Haemorrhage also causes a redistribution of intracellular fluid (Stewart and Rourke, 1936; Landis and Johnson, 1942). Thus this compartment helps maintain an adequate plasma volume, and hence tissue perfusion. All the compartments are inextricably inter-related.

As will be discussed in greater depth later, it appears probable that not all groups of cells act in the same way, nor respond at the same time following a disturbance in extracellular electrolyte concentrations such as would occur in an experiment. Thus for example, the central nervous system cells act to protect their volume at the expense of the extraneural intracellular constitution (Pollock and Arieff, 1980). Following increases in plasma osmolality, the brain, like other tissues, shrinks as a consequence of fluid loss. However, in a matter of hours to days, restoration of brain volume may be achieved if the solute

initiating the original hyper-osmolality is endogenous, i.e. naturally found within the animal (Sodium ions, urea or glucose). This is due largely to the generation of new non-electrolyte solutes within the brain (Pollock and Arieff, 1980). These solutes only appear when the hyperosmolality is caused by endogenous substances. The application of such substances as mannitol or glycerol does not result in the production of these new substances and the brain consequently remains dehydrated.

In hypo-osmolal states, the brain increases in volume, as do other body tissues, but not to such an extent. In time, brain cell volume is again restored, largely as a consequence of intracellular electrolyte loss (i.e. Potassium and Sodium) (Pollock and Arieff, 1980).

Pollock and Arieff (1980) discuss the consequences of this unique behaviour in the light of various clinical states. In the current context however, it would be interesting to see whether their findings are relevant to studies of intracellular-induced drinking motivation. Perhaps further use of simulations such as the one presented here could help elucidate the issues and suggest possible experimental consequences.

As discussed earlier, the flow of intracellular fluid across the cellular boundary is assumed here to be purely a function of osmotic pressure gradients. Unlike the vascular and interstitial compartments, there does not appear to be any intracellular volume/pressure function, at least in animals. The cellular boundary is a very fragile structure, and could not tolerate any significant pressure. Indeed, one

of the most important functions of the Sodium pump (see below) is to prevent continual swelling of the cells.

The many organic substances produced within the cells are frequently incapable of diffusing across the cell boundary. These substances therefore exert an osmotic pressure, attracting fluid into the cellular milieu. Without some means of correcting this tendency, the cells would swell and eventually burst. Plants on the other hand, with their cellulose-reinforced walls, may well have volume/pressure relationships.

As the flow of fluid from the intracellular compartment is inextricably related to the flow of inorganic ions, the two systems are described in this one section.

System Description

Blocks 1 to 7 (see Figure 6.1) represent the intracellular metabolism of Potassium. Block 1 calculates the rate at which Potassium ions enter the intracellular compartment from the interstitial fluid (DICK1, mg/s). It is assumed that the rate of ingress is directly proportional to the ion's interstitial concentration. Block 2 calculates the corresponding loss rate of Potassium ions from the intracellular compartment (DICK2). Again the assumption is that the loss rate is directly proportional to concentration. In addition, Potassium is actively transported into the intracellular compartment by means of the Sodium pump. Consequently, the constant determining Potassium flow into the intracellular compartment (block 1) is larger than that in block 2 determining its loss. However, it should be borne in mind that under equilibrium conditions the ion flow into the intracellular compartment equals the flow out, due to the unequal normal concentrations on either side of the intracellular/interstitial boundary. Thus, under these circumstances, net flow is zero.

This system is obviously something of a simplification. For example, Bia and DeFronzo (1981) showed that during the few hours following an acute plasma load of Potassium only about 50% is excreted by the kidneys. Of the remainder, most is translocated into cells. This response, possibly mediated by insulin and epinephrine, provides the main means of defence against hyperkalemia.\* Epinephrine is further implicated in extra-renal Potassium homeostasis by the

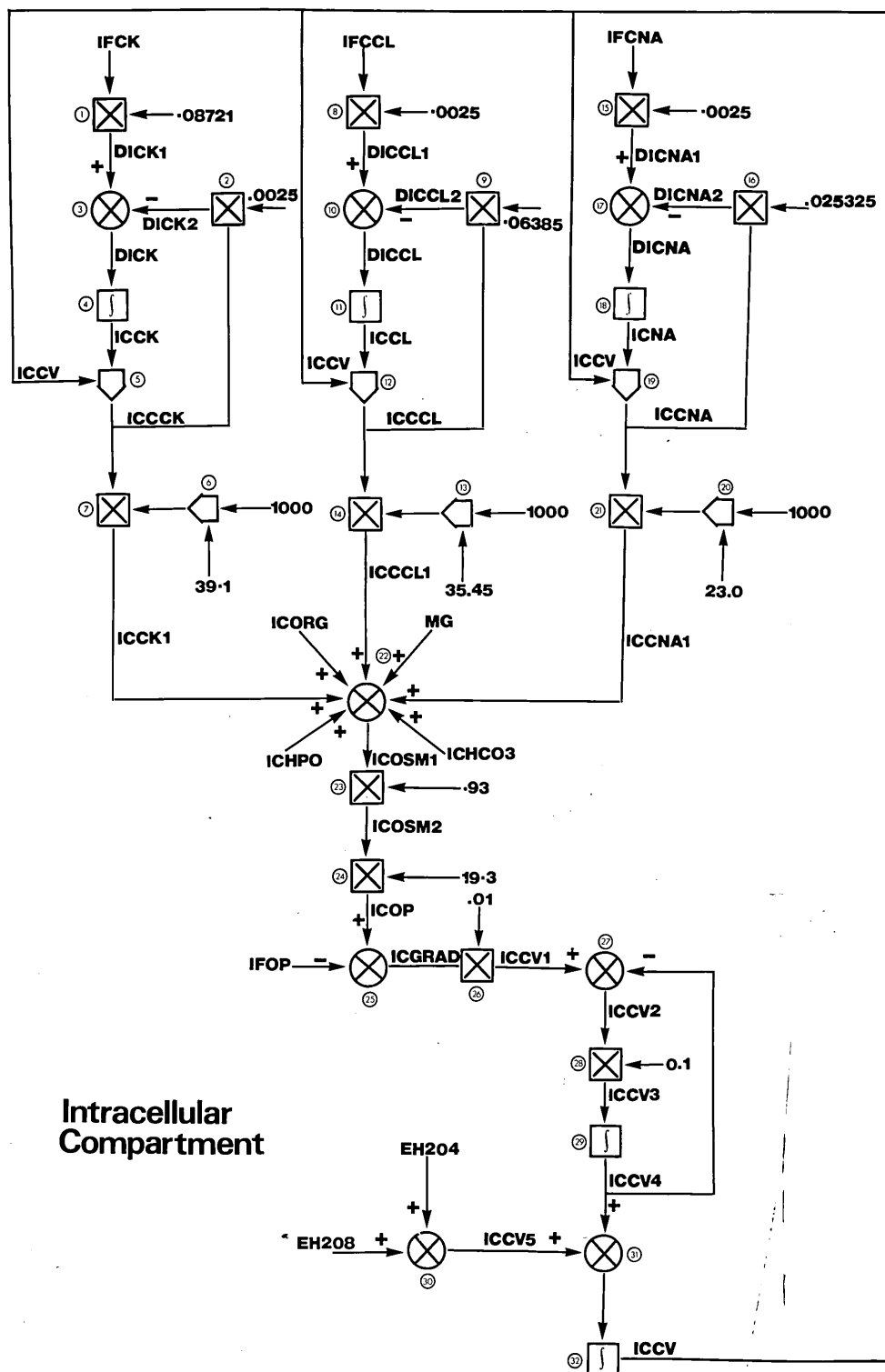


FIGURE 6.1

findings of Silva and Spokes (1981). These authors showed that uptake of Potassium by the intracellular compartment is modulated at least in part by peripheral sympathetic activity.

Block 3 calculates the net rate of loss or gain of Potassium (DICK), whilst block 4 integrates this signal to give the total intracellular content of Potassium (ICCK). Block 5 divides this content by the volume of intracellular fluid (ICCV), yielding intracellular Potassium concentration (ICCKC).

Blocks 6 and 7 are responsible for converting this concentration from mg/ml to mOsmoles/liter. The constant of 39.1 in block 6 represents the atomic weight of Potassium. The value of 1000 converts the volume unit from ml to l.

Blocks 8 to 14 represent the intracellular turnover of Chloride ions. Except for the constants determining ion flows in and out of the intracellular compartment, the system design is identical to that for Potassium, and thus will not be described in depth. Note however that the constants in blocks 9 and 10 (analogous to blocks 1 and 2 in the Potassium system) are the 'other way around'. This reflects the active transport of Chloride ions out of the intracellular compartment, rather than in. This is also the case in the Sodium system (blocks 15 to 21). The constants employed here have been empirically derived for the purposes of this simulation, and take into consideration the relative

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\* This raises the possibility that at least some of the intracellular Potassium loss observed during food deprivation (e.g. Elkinton and Winkler, 1944) may be a response to reduced insulin levels.



intracellular and extracellular ion concentrations, as well as the time taken for equilibrium to be achieved following a disturbance of the steady state. Data relevant to this latter topic is not readily available, but it was felt that the study of Flexner et al (1944) is applicable.

Block 22 calculates the total concentration of osmotically active substances within the intracellular compartment. As well as the regulated ions, i.e. Potassium, Sodium and Chloride, this also represents the influences of organic substances (ICORG), phosphate (ICHPO), bicarbonate (ICHCO3) and Magnesium (MG) ions. The values used are derived from Guyton (1976), p.432. Blocks 23 and 24 convert the total intracellular osmolality derived in block 22 to the appropriate osmotic pressure. All molecules and ions in solution exert either intermolecular attraction or repulsion. These can cause respectively a decrease or an increase in the osmotic activity of the dissolved substances, relative to the sum of the individual activities. Generally there is more attraction than repulsion, thus the overall osmotic activity of the substances is only about 93 per cent of that which one would calculate from the mixture's osmolality. This is the reason for the constant shown in block 23. The actual osmotic pressure of a solution (in mmHg) at body temperature can be determined approximately by multiplying the solution's osmolality by 19.3. This is derived by block 24. (Guyton 1976, p.432).

Block 25 subtracts interstitial fluid osmotic pressure from intracellular osmotic pressure, to give the osmotic

pressure gradient across the cellular boundary. This is the major determinant of fluid flow into or out of the intracellular compartment. Block 26 represents the 'permeability coefficient', converting the pressure gradient to actual fluid flow rate. The constant used was derived empirically, using the assumptions that fluid equilibrium between an individual cell or group of cells following a disturbance would take about one minute at most, and that the burden of restoring this equilibrium would fall equally on ion and water transport. These assumptions are lent some credibility by the findings of Hevesy and Jacobsen (1940), in their rabbit studies. However, blocks 27 to 29 impose an exponential delay on this flow rate. This represents the fact that not all cells in the body respond at the same time following a fluid disturbance, as a consequence of the imperfect communications between and within the body compartments. Thus one section of the body's millions of individual cells may be responding to a disequilibrium before another section has even been disturbed. Essentially, it is a consequence of the 'particulate' nature of the intracellular compartment, alluded to earlier in this section. To summarise therefore, although the system in blocks 26 to 32 will respond in an exponential manner anyway, it is necessary to add an additional delay, to represent the fact that not all parts of the intracellular compartment receive a stimulus at the same time.

Block 30 sums water losses or gains due to energy metabolism. These may be due either to the metabolic water derived from the breakdown of food (EH204), or the movement

of water physically bound with glycogen, fat or protein energy reserves (EH208). For further details, see the section on energy metabolism. Block 31 sums both metabolically- and osmotically-induced shifts of water, to give the total flow rate. Block 32 then integrates this signal, giving the volume of intracellular water (ICCV). As in other parts of the simulation, fluid flows are expressed in ml/s, and thus volumes of fluid are in ml.

#### Validation of the Intracellular Compartment

No separate validation is offered here; it is adequately analysed in both the 'small rat' and 'large rat' simulations presented elsewhere.

Some Notes on the Neural Intracellular System

Earlier, in the section describing the intracellular compartment, it was pointed out that this 'compartment' is in fact comprised of an enormous number of separate entities. The fact that on average this conglomerate of cells respond in a similar way to a stimulus, enables one, for some purposes, to treat it as a single entity.

Nevertheless, this approach can trap the unwary, for it forces one to treat the behaviour of the intracellular compartment as a unitary phenomenon. This may be valid when considering the behaviour of the mass of cells as in, say, dehydration over a period of hours. However, it is not a valid assumption when one is interested in the behaviour of a small sample of the cellular population. This misconception has influenced underlying attitudes towards the nature of the intracellular stimulus to drinking (and hypophyseal hormone release) for some years. It has long been apparent that the neurones representing cellular hydration are localised, but the possible theoretical significance of this localisation has received scant attention. This has been particularly true in the case of systems approaches to drinking motivation (e.g. Toates and Oatley, 1970), which really should have known better. To date, it has been all too easy to regard the body compartments as homogeneous masses, which is obviously not the case. Just as it takes time to transport fluid and electrolytes from one compartment to another, it also takes time to transport them within any one compartment.

It appears that the intracellular-induced motivation to

drink is mediated by osmoreceptor cells, located in the anterior hypothalamus and preoptic region (Jewel and Verney, 1957). Peck and Novin (1971) suggested that the osmoreceptor site for drinking (at least in the rabbit) was the lateral preoptic area. Similar findings for the rat have been reported by Blass and Epstein (1971) and Blass (1974). Although much remains to be resolved, this does appear to be the general area of the brain most likely to be involved. The case for the supraoptic nucleus being a site for osmoreception is well argued by Leng, Mason and Dyer (1982).

There are also good arguments for a number of peripheral osmoreceptors, particularly in the hepatic-portal system. Such receptors were originally studied in relation to the release of anti-diuretic hormone (Haberich, 1968), but evidence now exists relating them to drinking motivation as well. Thus for example, hepatic infusions of hypertonic saline induce drinking (Kozlowski and Drzegiecki, 1973). These peripheral signals appear to be transmitted via the vagus nerves, as vagotomy modifies the effect (Kraly, Gibbs and Smith, 1975; Smith and Jerome, 1983).

Both the supraoptic nuclei and liver are very densely vascularised, receiving a rich supply of blood. These receptors have usually been regarded as being representative of cells within the rest of the body. This is probably true to the extent that they respond to the same types of stimuli. But because they are sited in such densely vascularised parts of the body, they would respond more quickly to plasma-mediated stimuli than would the rest of the cells in the body. Thus they are not 'representative

cells' in the sense that Mayer (1900) would have regarded it.\* Rather, they are cells that give early warning of changes to the main mass of body cells. The possible theoretical significance of this is discussed later. The consequence of immediate relevance to the current topic however is that intracellular behaviour 'per se' is not an adequate analogue to the signals received by the brain indicating hydrational state. As stated earlier, this was a crucial failing of this simulation's predecessors, e.g. Toates and Oatley, (1970).

Therefore the simulation presented here incorporates a 'tiny intracellular compartment' (actual volume somewhat arbitrary, but around .05 ml), to represent the differing response characteristics of the osmoreceptors. This small compartment has been termed, for want of a better name, the 'neural intracellular compartment'.

The system developed to represent the behaviour of the neural intracellular compartment is somewhat novel, and is thus explained in a separate section, entitled 'The nature of the intracellular stimulus to thirst' (see Chapter 15).

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\* For excellent discussions of the history of thirst research, see Fitzsimons (1979) or Rolls and Rolls (1982).

CHAPTER 7The Control of Drinking and FeedingDrinking Stimuli and their Interactions

Gilman (1937) demonstrated that a critical stimulus for drinking following dehydration is loss of water from inside the cells. He found that administering hypertonic solutions of substances that cannot cross the cell wall stimulates drinking, because they cause a loss of water from inside the cells by osmosis. Although, as is discussed elsewhere, controversy continues to this day about the nature of the intracellular stimulus to drinking, all are agreed on the fundamental point that withdrawal of water from the intracellular compartment induces drinking. This withdrawal naturally causes an increase in concentration of the intracellular solutes. Thus any realistic theory of drinking has to incorporate some representation of intracellular state in its decision-making system. Such is the case here. The exact nature of the intracellular stimulus to thirst is discussed in Chapter 15.

Loss of extracellular fluid has also been shown to initiate drinking. Thus clinically, haemorrhage is found to lead to drinking (Wettendorff, 1901- humans). This is also the case in rats (Fitzsimons, 1961b); water intake subsequent to haemorrhage is directly proportional to the fluid lost (Russell, Abdelaal and Mogenson, 1975). These findings have been corroborated by the rather more elegant

technique of polyethylene glycol (PEG) administration (e.g. Stricker, 1968). None of the extracellular interventions should greatly affect the intracellular compartment; thus there must be, independent of the intracellular stimulus to thirst, an extracellular mediator.

Although there is some confusion about the issue, there appear to be several mediators of extracellular hypovolemia. It is hoped that this confusion may be at least partly resolved by the system presented here.

Fitzsimons (1969) found that ligating the inferior vena cava (rat) resulted in a marked increase of water intake and a decrease in urinary output. Subsequent studies (e.g. Fitzsimons and Moore-Gillon, 1980a and b) have shown that the renal renin-angiotensin system makes an important contribution to such caval ligation-induced drinking. In addition, Fitzsimons and Simons (1969) showed that intravenous infusions of angiotensin II into normal rats stimulates copious drinking, probably by direct action on central nervous receptors (Epstein, Fitzsimons and Rolls, 1970).

However, not all of the drinking subsequent to hypovolemia can be accounted for in terms of increases in the level of circulating angiotensin. For example Lee, Thrasher and Ramsay (1981), found that the renin-angiotensin system alone does not play an essential role in the control of drinking after water deprivation or caval ligation in rats. Removing both kidneys, which eliminates changes in circulating angiotensin, has little effect on drinking induced by polyethylene glycol (Stricker, 1973), or water



deprivation (Rolls and Wood, 1977). Thus drinking induced by these techniques has been attributed to changes in activity of atrial receptors. These atrial receptors appear to have a direct effect on drinking, although they do also stimulate the renin-angiotensin system. Further evidence for this direct effect of atrial receptors is provided by Ramsay, Rolls and Wood (1975). They found that the infusion of saralasin acetate (which blocks angiotensin activity) reduces, but does not abolish drinking induced by thoracic caval ligation. This latter experiment was conducted on dogs. Thus it seems reasonable to conclude that to date three 'central' dipsogenic stimuli have been discovered; one intracellular, the exact nature of which is not certain, and two extracellular (atrial receptors and plasma angiotensin).

How do these stimuli interact in normal drinking? Water deprivation is probably the commonest model for this, and has been widely studied.

Rolls, Wood and Rolls (1980- rats) showed that removal of the cellular thirst stimulus (by preloading the vasculature with water) reduces deprivation-induced drinking by between 64 and 69 per cent. Alternatively, removing the extracellular stimuli (with isotonic saline preloads) reduces deprivation-induced drinking by between 20 and 26 per cent. How much of the extracellular contribution to deprivation-induced drinking can be attributed to angiotensin, and how much to atrial receptors?

Perhaps surprisingly, removal of the renin-angiotensin system in rats does not reduce deprivation-induced drinking (Rolls and Wood, 1977). Similarly, the administration of

saralasin into the ventricles of dogs (Ramsay and Reid, 1975), sheep (Abraham, Denton and Weisinger, 1976) and rats (Lee, Thrasher and Ramsay, 1981) failed to affect deprivation-induced drinking. Thus removal of the renin-angiotensin system, by a variety of means, does not appear to influence deprivation-induced drinking. However, the increase in plasma angiotensin concentration observed during water deprivation is similar to that which results from intravenous doses known to elicit drinking (Mann, Johnson and Ganten, 1980).

The studies cited above suggest that angiotensin is not essential in deprivation-induced drinking. However, as Rolls and Rolls (1982) point out, this is not to say that angiotensin does not normally have a role to play. It may well be that in drinking, as in other physiological systems, there is a redundancy of mechanisms. Thus when one is removed, others take over (Rolls and Wood, 1977). Some evidence for this is presented by Hoffman, Ganten et al (1978). They found that blocking either angiotensin receptors (which they suggested mediate extracellular drinking stimuli) or cholinergic receptors (intracellular stimuli) had no effect on deprivation-induced drinking. However, combined blockade of both types of receptor reduces drinking by 70 per cent. They concluded that the two receptors are independently capable of maintaining thirst.

Traditionally, the various stimuli to drinking are considered to be additive, as originally suggested by Corbit (1968) and Fitzsimons and Oatley (1968). Yet here one is faced with a situation which could not be predicted by a

simple theory of additivity. This theory would predict that following the blockage of one stimulus, drinking elicited would decrease by a similar proportion. The only means by which an additive system could produce results such as those given here is if the total stimuli increase in magnitude until the remaining mediators are capable of exceeding the threshold value, beyond which drinking is initiated. This cannot be the case in dehydration studies, in which the period of water deprivation is fixed; water is made available after this pre-determined interval, and there is no opportunity for any stimuli to further increase in magnitude. A variety of systems, all essentially based on additivity, could be designed to conform to these findings. For example, one could postulate a system that lowered the drinking 'threshold' whenever one of the three drinking stimuli were blocked. However, it is felt that this is unlikely. On the basis that one should design theoretical control systems that not only conform to the known data but also adhere to realistic physiological principles (to say nothing of parsimony), the model just described would appear difficult to describe in terms of neuronal interactions.

Neurons interact with each other in a variety of ways. Thus one nerve cell can act to enhance the probability of another firing (excitatory). However, they can also act to inhibit the probability of other cells firing. Using these two principles alone, one can create a system that can encompass the findings of the dehydration experiments described above.

The essential idea of this system is that each

participating stimulus to drinking is not only added to each other; they also exert an inhibitory effect on each other (see Figure 7.1). As long as all the contributing stimuli are intact, then the appearance given is one of strict additivity. However, blockage of one of the three stimuli, whilst obviously removing some of the additive influences, also removes some of the inhibitory influences on the remaining two stimuli. The magnitude of these remaining stimuli consequently increases, compensating for the loss of the third. This, it is felt, could explain why blockage of the renin-angiotensin system appeared to have no effect on deprivation-induced drinking. On the other hand, subpressor angiotensin infusions at physiological levels do influence drinking, because such experiments do not abolish any of the drinking stimulus systems. More recent evidence suggests that angiotensin is indeed involved in dehydration-induced drinking, especially following long periods of deprivation (Barney, Threatte and Fregly, 1983- rat), although contradictory reports still appear (e.g. Lee, Ramsay and Thrasher, 1981- rat). Perhaps the drinking systems are incapable of compensating adequately when an individual component's contribution exceeds a certain degree. Interestingly, Barney et al (1983) employed captopril (an angiotensin I converting-enzyme inhibitor), whilst the negative report of Lee et al (1981) employed saralasin, a competitive blocker of angiotensin II binding sites.

Abolition of two of the three stimuli presents the drinking system with an impossible situation. Here, although



all inhibition on the sole survivor is removed, it cannot increase sufficiently in magnitude to compensate. Hence the drinking response to dehydration is attenuated.

It must be stressed that the system presented here is somewhat speculative; much yet remains to be discovered, which will doubtless in time render the theory unrealistic. For example, what is the role of bradykinin in dehydration-induced drinking (Lewis, Hoffman and Phillips, 1983)? Similarly, does anti-diuretic hormone have a significant effect (Schwartz and Reid, 1983)? However, if this theory provokes thought and controversy, then its principal aim will have been achieved.

The summed signal emanating from the drinking system is compared with a 'threshold' value, derived empirically. When the stimulus signal exceeds the threshold, then drinking is initiated. Drinking continues (at a rate of .03 ml/s) until either intestinal content of fluid exceeds 10 ml or the stimulus ceases to exceed the threshold. The rate of drinking employed here represents a mean value of those given by Stellar and Hill (1952), Corbit and Luschei (1969), and Hall and Blass (1975). Naturally, all studies cited are of the rat. Since the drinking stimulus arises from what would normally be considered as 'central' receptors (i.e. generally vascular), there is a delay between ingestion of water and its subsequent effects. This 'inbuilt' delay precludes the need for resetting the threshold at a lower value once drinking starts, a technique employed by Toates and Oatley (1970). It is conceded that this decision-making system is somewhat simplistic, but it appears to be adequate

for providing a reasonable water intake for the animal. Future systems will attempt to represent oro-gastric influences on drinking, as in the 'small rat' simulation. In this respect, the 'small rat' is in advance of the 'large rat' simulation. Consequently, the current model is unlikely to be able to cope with such phenomena as the effects of gastric distension on drinking.

Several models to determine the initiation of drinking can be designed. For example, one could employ signal detection theory. This, by imposing random 'noise' upon the drinking stimulus prior to comparison with the threshold value, renders the predictions made somewhat probabilistic, as is the case in experimental animals. (For a brief description of signal detection theory, see Hilgard, Atkinson and Atkinson, 1971, p.111, or Lindsay and Norman, 1977, p.715). Once drinking is initiated by the above-mentioned system, the amplitude of the noise signal is reduced, to emulate (if one will forgive the anthropomorphism) the animal giving attention to the task in hand. This causes the animal to 'lock on' to the task in hand. In all probability, such a system could be made very realistic, but it is felt that such efforts may be misguided; there is little physiological basis for it, and as Weiskrantz pointed out (Chapter 1), it is easy to create any number of different models that predict the same results, unless one is able to root that model in sound physiological principles.

Another system designed during the development of the current simulation was based upon catastrophe theory

(Zeeman, 1979). In effect, this really represents a three-dimensional version of the threshold model used by Toates and Oatley (1970). The additional dimension in the catastrophe theory model was devoted to representing the accessibility of water. Thus when water is difficult to obtain (perhaps owing to distance, or the necessity of crossing an electrified grid), the animal will tolerate a greater degree of privation. The drinking pattern will essentially be one of a small number of large drinks. On the other hand, when water is always readily accessible, the drinking pattern will consist of a large number of small drinks. Again, whilst such a system may well be realistic in its predictions (and no close examination has been made in this respect), it is felt that it is descriptive, rather than explanatory, and such is not the aim of the current project. The same could be said of yet another system briefly considered, based upon the micro-economic theory of supply and demand. Put simply, the greater the stimulus to drinking, then the greater the 'price' (in terms of effort, risk of predation etc.) an animal is willing to pay for satisfaction of that demand. For all their intellectual appeal, such an example only serves to emphasise the point that many theories actually represent only the merest analogy to reality, and have no explanatory depth. At best they can form useful conceptual frameworks, pending the availability of better analyses; however, they are just as likely to be misleading, and induce fruitless research.

The more one studies the systems subserving drinking, the more one appreciates how fundamental water is to the



overall performance of animals, and thus the multiplicity of systems participating in the regulation of its ingestion and excretion. Surely, this is a subject in which a multi-disciplinary, systems-based analysis is essential for a proper understanding.

#### Validation of the Drinking System

Apart from the arguments presented in this Chapter, the drinking system is analysed in greater depth in Chapter 14. This, it is hoped, provides further validation (or otherwise!) of this system.

Meal Scheduling

The particular aim of the present study is to analyse fluid metabolism in the rat. Thus it was considered that a realistic representation of food intake regulation was outside the scope of the current project. To have tackled feeding motivation as well as drinking would have been more than one could hope to achieve in the time available.

Thus in this particular simulation, the regulation of food intake is not determined by factors intrinsic to the model. Consequently it was necessary to create an artificial feeding pattern that realistically emulated the pattern one would normally expect to see in a laboratory rat. The aim of this chapter is to justify the pattern adopted.

Estimates of total 24 hour food intake for a rat of about 300g weight are generally between 22g and 25g (Siegel and Stuckey, 1947; Booth, 1972; Panksepp, 1973; LeMagen, 1981). These figures apply for a diet consisting of a typical 'lab chow'. The constitution of these vary somewhat, according to the proportion of grain incorporated etc., but the analysis used in this simulation is representative, being for Spiller's Small Animal Diet.

21.0%	Protein
48.0%	Digestible carbohydrate
5.0%	Oil (fat)
0.3%	Na+
1.3%	K+
0.8%	Cl
0.9%	Ca++
6.0%	Water
16.7%	Other (treated as indigestible)

These data are the source of the constants used in the simulation to convert food intake to stomach input of individual constituents.

Most of the daily food intake is eaten at night, with peaks immediately after the start and before the end of the dark period. This 'bimodal' distribution of food intake was first observed by Siegel (1961), and has since been corroborated many times (e.g. LeMagnen and Devos, 1980).

Both meal sizes and distribution vary throughout the day. Rats tend to eat large and frequent meals during the dark (active) phase, but small and infrequent meals during the day (LeMagnen, 1981). Thus a typical rat would eat about eight meals during the night, with an average size of 2.5g, but only three meals during the day, each of about 1g (LeMagnen and Devos, 1980).

The rate at which food is eaten also varies between night and day, as well as whether the food is powdered or unpowdered. However, data from Booth (1972) suggests a general intake rate of around 150 mg/minute, somewhat less

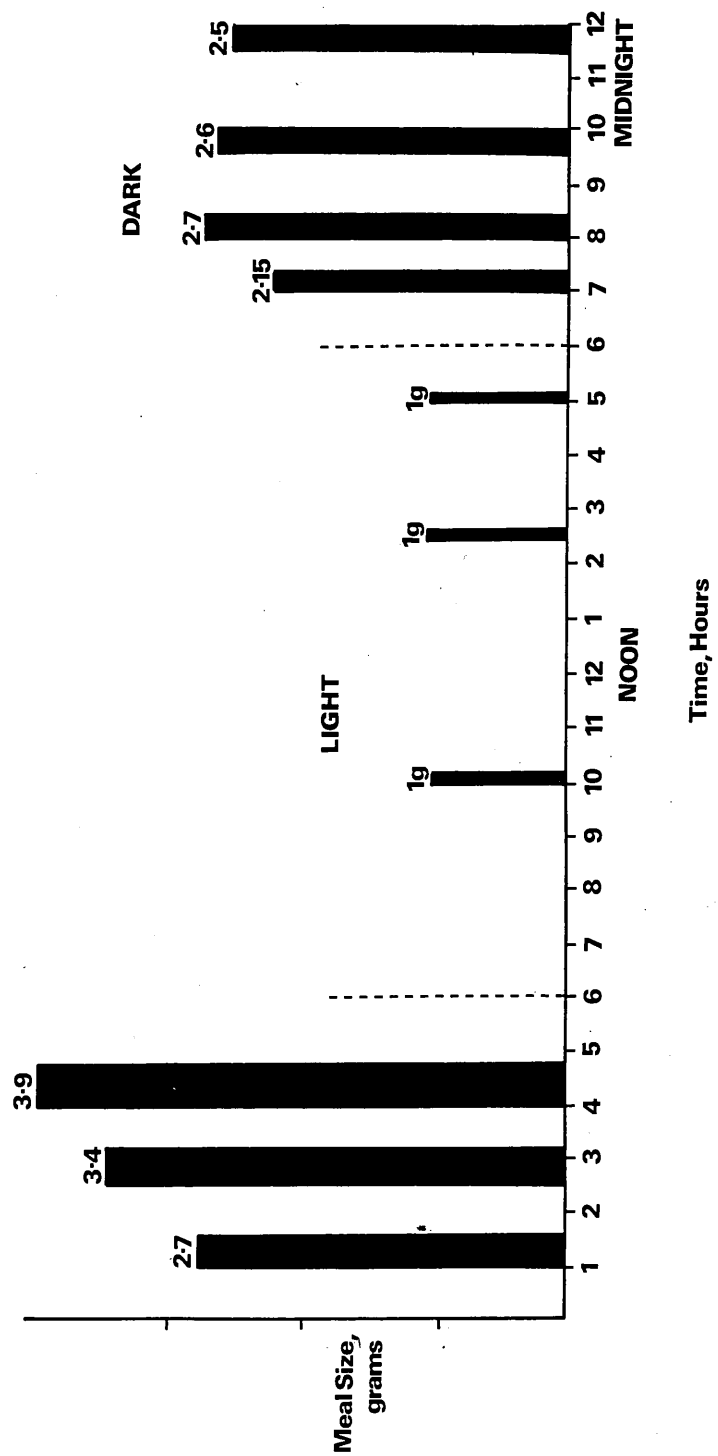


FIGURE 7.2

then the later estimate of Booth, Toates and Platt (1976) of 300 mg/minute. However, somewhat more detailed information is available from LeMagnen and Devos (1980). They show that with allowance for pauses made whilst eating, daytime intake rate is about 110 mg/minute; the corresponding rate at night is 90 mg/minute. Interestingly, when the effects of pauses are removed, this slight tendency for faster daytime eating is reversed; it is now 180 mg/minute, compared with a night-time rate of 200 mg/minute.

The resulting representative eating pattern used in this simulation is presented in Figure 7.2.

CHAPTER 8The Gastro-Intestinal Tract and Energy MetabolismThe StomachIntroduction

Stomachs vary widely in structure and function. For example, in man it is merely a one-cavity organ whose main function is to regulate food delivery to the intestine. At the other extreme the stomach of the ruminant has many cavities, in which much of the food is digested.

Rodents occupy an intermediate position. The hamster possesses a two-compartment stomach; the rat however has a one-cavity stomach in which the two parts are visibly different. The pars cardiaca, or forestomach, is provided with a cutaneous mucous membrane without glands. The pars pylorica on the other hand has a typical glandular mucous membrane.

The specific roles, if any, of the two sections in a rat stomach are unclear. Kunstyr, Peters and Gartner (1976) have shown that the digestive performance of rats with surgically removed forestomachs differs from that of the non-operated controls. However, these cannot have been serious differences, as the operated rats survived without complications for at least one year following surgery. Thus it would appear that the digestive abilities of the rat stomach are limited, and need not be considered in the simulations presented here.

### System Description

Generally, the substances that the stomach has to deal with may be divided into three categories. They are water, electrolytes and food. The latter two are further subdivided as necessary. Although they are all inter-related, this description shall treat each in turn. The whole system is illustrated in Figure 8.1.

### Stomach Water

The basic concept of the stomach systems used in both models is as presented by Toates (1971), in which he states;

"The stomach performs the mathematical process of integration on the flow rate of water drunk. Water can leave the stomach by means of the pyloric sphincter or by osmotic absorption across the stomach wall."

Furthermore, following a preload of water, the volume remaining in the stomach appears to decay as an exponential function of time, in both rats (O'Kelly, Falk and Flint, 1958) and humans (Evans, 1949, p.873). It is felt however that this finding only holds true when all other factors that determine stomach content release are held constant. Thus a control system, if justified by the goals of the overall model, should be designed so that it can cope with variations in most determinants of stomach emptying, such as stomach content osmolality and viscosity, as well as plasma osmolality.

Most of the water ingested by a rat is normally 'free',

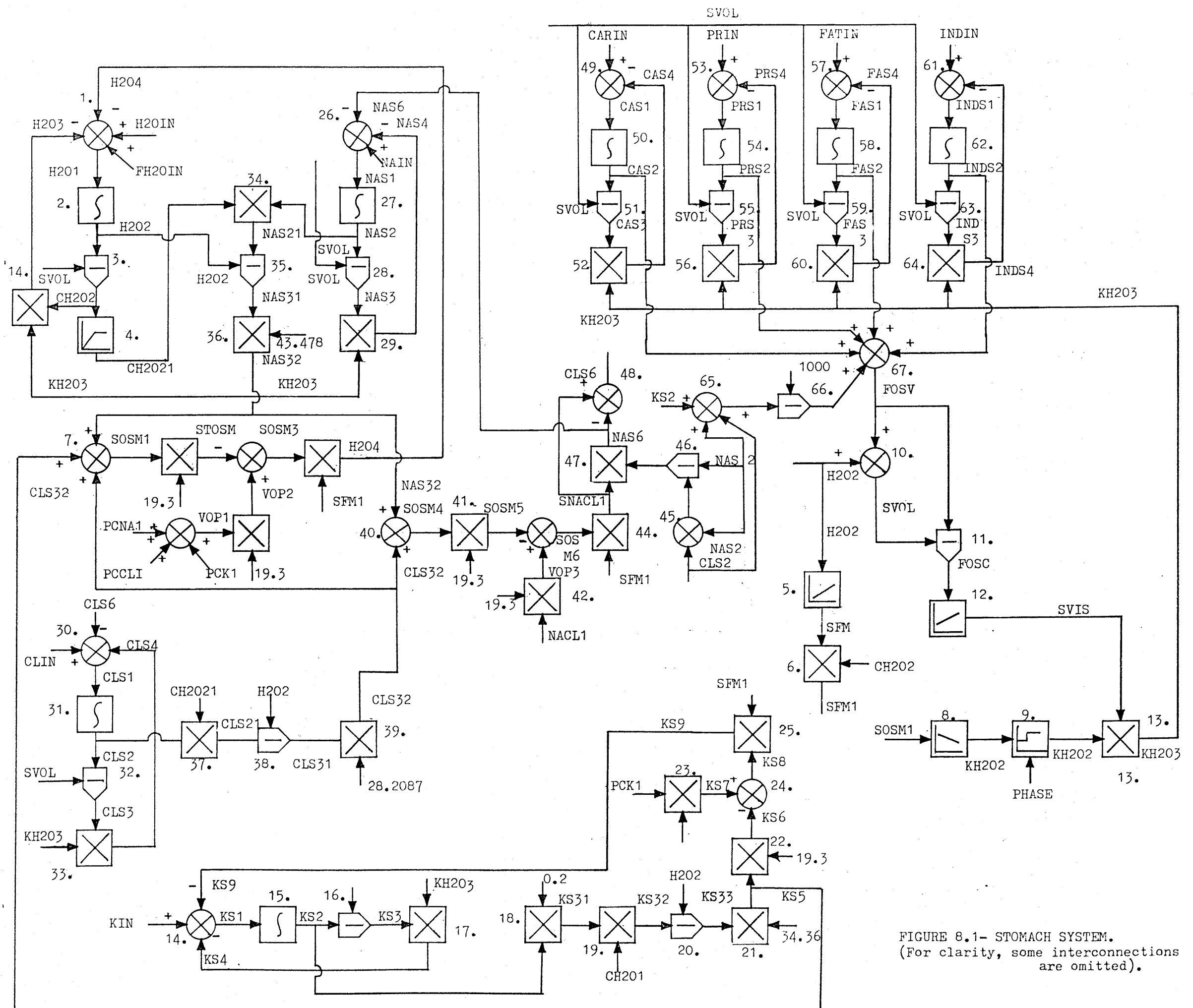


FIGURE 8.1- STOMACH SYSTEM.  
(For clarity, some interconnections are omitted).



drunk by the animal in response to a perceived water deprivation (H2OIN). All foods however contain a fraction of water, and thus some is inevitably delivered to the stomach as a consequence of eating. This is represented in block 1 by FH2OIN, ml/s.

As discussed earlier, losses of water from the stomach can occur by delivery to the intestine (H2O3), or osmotic absorption (H2O4). All these effects are summed in Block 1, to give the net flow of water in any one moment (H2O1, ml/s). This signal is then integrated in Block 2 to give stomach water content (H2O2, ml).

Losses of water from the stomach are determined by a range of factors, many of which also influence the loss of food and ions.

Osmotic transfer of water across the stomach wall can occur in either direction. Thus placing a hypertonic solution or food with a high inorganic ion content in the stomach will induce a flow of fluid from the vasculature, and result in a net gain of stomach water.

The final arbiter of this transfer is the osmotic pressure gradient across the stomach wall, represented in this simulation by the vascular and stomach content concentrations of Sodium, Chloride and Potassium ions. However, when deriving stomach osmotic pressure, it is considered that several complicating factors arise.

In practice, the vast majority of inorganic electrolytes are ingested with food. During the course of program development, it was found that the sudden release of all these ions, especially Potassium, into the available

stomach water produced quite unlikely concentrations, considering the amount of water that would of necessity be drawn into the stomach by the resulting osmotic pressure. Thus it appeared reasonable to assume that the release of ions from food to free water was a more gradual affair, related to the availability of free water, i.e. the ratio of food matter to stomach water. Below a certain ratio, the contact between water and food cannot be sufficiently intimate to guarantee solution and distribution of all inorganic ions. This may be particularly true in the case of Potassium, which is predominantly held within the cells of which the food is comprised.\* This system is embodied in blocks 3 and 4. The relationship between stomach content/stomach water ratio and the ease with which inorganic ions can be released is somewhat arbitrary, but one hopes it is a reasonable representation. The actual osmolality of the stomach's fluid contents is derived by summing the concentrations of Potassium, Sodium and Chloride ions, as shown in block 7.

Finally, the actual rate of fluid flow across the

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\* This could lead one to speculate about the validity of comparisons between the intestinal effects of 'ordinary' food, such as grain and meat, and the ubiquitous laboratory chow on osmotic transfer of fluid. It is possible that the dessicated nature of laboratory chow so destroys the cell walls of the grain of which it is mainly comprised that release of intracellular electrolytes is much more rapid than would be the case with 'ordinary' foods. In these, the cell walls would still be relatively intact, despite the process of mastication. The characteristics of inorganic ion release and thus fluid flows across the stomach and intestine walls would be quite distinct. Given that the loss of vascular fluid to the gastro-intestinal tract can be a potent stimulus for drinking, examining the nature of any such differences could be an interesting project.

stomach wall is directly proportional to the area over which exchange can occur. This is represented by the 'stomach filling multiplier' (SFM1). (Blocks 5 and 6). In this simulation, one is normally dealing not merely with fluid, or electrolyte solutions, but mixtures of food, water and ions. Under these conditions, the stomach wall area which is directly in contact with water is determined both by the total amount of mixture in the stomach, and the proportion of that mixture that is water. Evidence for the existence of such a 'filling multiplier' is provided by Cope, Blatt and Ball (1943), who showed a negatively accelerating curve for absorption of water across the stomach wall. The extent to which such a relationship would be linear, especially when dealing with mixtures of food and water, is unclear. However, it is anticipated that the function shown in block 5 is a reasonable approximation.

The rate of water delivery to the intestine is also influenced by the amount of water in the stomach, as one would expect, and in a different manner, by the osmolality of the stomach contents (SOSM1- block 8). There are additional influences, however. These are day/night phase (block 9) and the viscosity of the stomach contents (blocks 12 and 13). It is considered that the latter influence is particularly significant when dealing with mixtures of food and water, rather than water alone. There does not appear to be a great deal of information available to assist in the development of a sub-system representing stomach content viscosity. However, a somewhat hypothetical description is incorporated. Validation of this hypothesis awaits

experimental data.

The relationship between the osmolality of stomach contents and delivery rate to the intestine is derived from that given by Toates (1971) p.103, and is here represented in block 8.

There is a great deal of evidence to indicate that stomach delivery rates of food to the intestine follow a circadian rhythm (Booth and Jarman, 1976; Booth, Toates and Platt, 1976). Essentially, the pattern appears to be that the rate of stomach emptying doubles at night (the rat's active period). This is represented by block 9.

The relationship between the viscosity of stomach contents and the rate at which the stomach would transfer these contents to the intestine is highly conjectural. However, it does seem to make sense that the more fluid the stomach contents are, the greater the ease with which they will flow into the intestine. The relationship finally derived to represent this tendency is shown in block 12. The system as a whole comprises blocks 10 to 13. Block 10 calculates the total volume of stomach contents, i.e. food, water and electrolytes (in ml). Block 11 then derives the ratio of total stomach volume (including water) to stomach dry matter content; this is the variable used for the calculation of stomach viscosity effects in block 12. It can be seen that the relationship is not linear; it was felt that viscosity would not be dramatically affected provided there was adequate fluid available. Below a certain level however, ease of transfer could be greatly influenced by even small variations in fluid content. Admittedly, much of

this system is hypothetical. Anecdotal evidence is about all that has become available so far. For example, '[Stomach] emptying tends to be slower after a meal of mainly solid material compared with one of a more fluid nature.' (Duke's Physiology of Domestic Animals, ed. M.J. Swenson, 1970. Animal not specified, but definitely not a ruminant!)

In this system, the effect of stomach content viscosity on stomach emptying is expressed as a fraction of unity; block 13 relates it to the actual rate of stomach content delivery to the intestine. All that is then required is for block 14 to calculate how much of the mixture delivered to the intestine is actually water. The result is then fed back to block 1.

Stomach Electrolytes- Potassium, Sodium and ChloridePotassium

This electrolyte predominates over Sodium in the majority of laboratory rat diets. The Potassium system is also simpler than the joint system determining stomach Sodium and Chloride metabolism, and is thus best described first.

As with water, electrolytes within the stomach can be lost by osmotic absorption across the stomach wall; most however are lost by delivery to the intestine. Under normal circumstances, all potassium received by the stomach is as a component of food. Thus the rate of Potassium intake shown in block 14 (KIN, mg/s) is determined by multiplying eating rate of food and the proportion of that food that is Potassium. The output of block 14 represents the net Potassium (K+) flow rate into the stomach (KS1). This is then integrated by block 15 to give the total stomach K+ at any one time (KS2, mg).

The 'concentration' of K+ with regard to total stomach content (fluid and dry matter) is derived by block 16. Delivery rate of K+ to the intestine is then calculated in block 17. It is assumed that the mix transferred to the intestine is of the same constitution as the mix contained in the stomach. Thus the transfer rate for K+ (and all other stomach content constituents) is determined by the same factors as stomach water. This includes influences due to stomach content osmolality and viscosity, as well as day/night phase.

Osmotically induced shift of Potassium is derived in blocks 18 to 25. The  $K^+$  content of lab chow is very high, relative to Sodium; however, as was discussed earlier, not all of this is released to become osmotically active in the stomach. Thus in addition to the limitations on general electrolyte solution embodied in block 4,  $K^+$  must experience further constraints. Considering that  $K^+$  is predominantly held within the intracellular spaces of the cells comprising food, this is perhaps a reasonable suspicion. Consequently, block 18 ensures that only 20% of total  $K^+$  held within the stomach contents can become available to exert an osmotic pressure. This is obviously something of an oversimplification, but considering the paucity of information it is a reasonable working hypothesis. Block 19 further restricts the solution of  $K^+$  (as it does also Sodium and Chloride ions) under circumstances where there is a low proportion of stomach water to dry matter. This function has been described earlier, under the discussion of stomach water turnover.

Block 20 divides the available  $K^+$  by the amount of free stomach water to give fluid  $K^+$  concentration ( $KS_{33}$ , mg/ml). Blocks 21 and 22 then convert this concentration to an osmotic pressure. This, when compared with an appropriately converted value of vascular  $K^+$  concentration, gives the concentration gradient down which  $K^+$  will tend to flow. Block 25 then relates this gradient to an actual flow rate by reference to the 'stomach filling multiplier' (discussed earlier) and the concentration of  $K^+$  in all stomach contents (blocks 5, 6 and 25).

Sodium and Chloride Ions

The remaining two stomach electrolyte systems operate in a very similar manner to that just described for Potassium. External input of both generally occurs as a consequence of food ingestion, and both can be lost from the stomach as a consequence of osmotic transfer across the stomach wall or direct delivery to the intestine. Net influx of Sodium ( $\text{Na}^+$ ) is determined by block 26; the corresponding task for Chloride ions ( $\text{Cl}^-$ ) is performed by block 30. In each case the net influx is subjected to integration, to derive total stomach contents of the respective ions. Following calculation of ion concentration in total stomach contents, efflux to the intestine is calculated by reference to osmolality, viscosity and phase influences. These tasks are performed in blocks 27-29 and 31-33 for  $\text{Na}^+$  and  $\text{Cl}^-$  respectively.

Calculation of other ion shifts across the stomach wall is essentially performed in the same manner as for Potassium. However the calculations for both  $\text{Na}^+$  and  $\text{Cl}^-$  are performed by the same system. This does make the system somewhat more economical, but it must be admitted that this probably relates more to historical factors during program development than any particular rationale.

Blocks 34 to 36 calculate the stomach Sodium contribution to total  $\text{NaCl}$  concentration gradient, whilst blocks 37 to 39 do the same for Chloride ions. Blocks 41 and 42 sum the contributions to the concentration gradient due to  $\text{Na}^+$  and  $\text{Cl}^-$ , and convert it to the appropriate osmotic



pressure. Block 42 performs a similar task for the vascular NaCl concentration. The summed net flow of Na<sup>+</sup> and Cl<sup>-</sup> from or to the stomach is then calculated by 43 to 44, considering the usual factors of stomach filling and concentration in all stomach contents. Note that there is no limitation on NaCl solution except for the general one due to shortage of stomach water (block 4). This total flow is then apportioned between Sodium and Chloride according to their respective concentrations in all stomach contents. This is done in blocks 45 to 48. Admittedly, many of the systems and factors represented in this section of the model are hypothetical. However, it appears to work in a realistic manner, when compared with the existing experimental data of Armstrong, Clarke and Coleman (1978) (see later). Presumably, future studies will highlight areas where further improvement would be desirable.

Stomach food

Blocks 49 to 64 comprise the system that simulates the turnover of food in the stomach.

There are four separate (though identical in principle) subsystems, one for each of the major components in food; carbohydrate, protein, fat and indigestible material.

The input of each constituent is obtained by multiplying food intake rate and the constituent fraction. Net change in stomach contents is then calculated by subtracting delivery rate to the intestine from this constituent input. Blocks 49,53,57 and 61 describe this for carbohydrate, protein, fat and indigestible matter respectively. In each case, these signals are then integrated, to give the total stomach contents of each constituent. As was the case with stomach inorganic ions, the 'concentrations' of these food constituents with respect to total stomach contents is then calculated. The result, when multiplied by the appropriate variable, gives the flow rate from the stomach to intestine for that particular food constituent. As discussed earlier, this variable incorporates such influences on stomach emptying rates as food osmolality and viscosity, as well as day/night phase.

Blocks 65-67 are responsible for calculating stomach dry matter content. Block 66 is a scaling factor to convert ion content from mg to g.

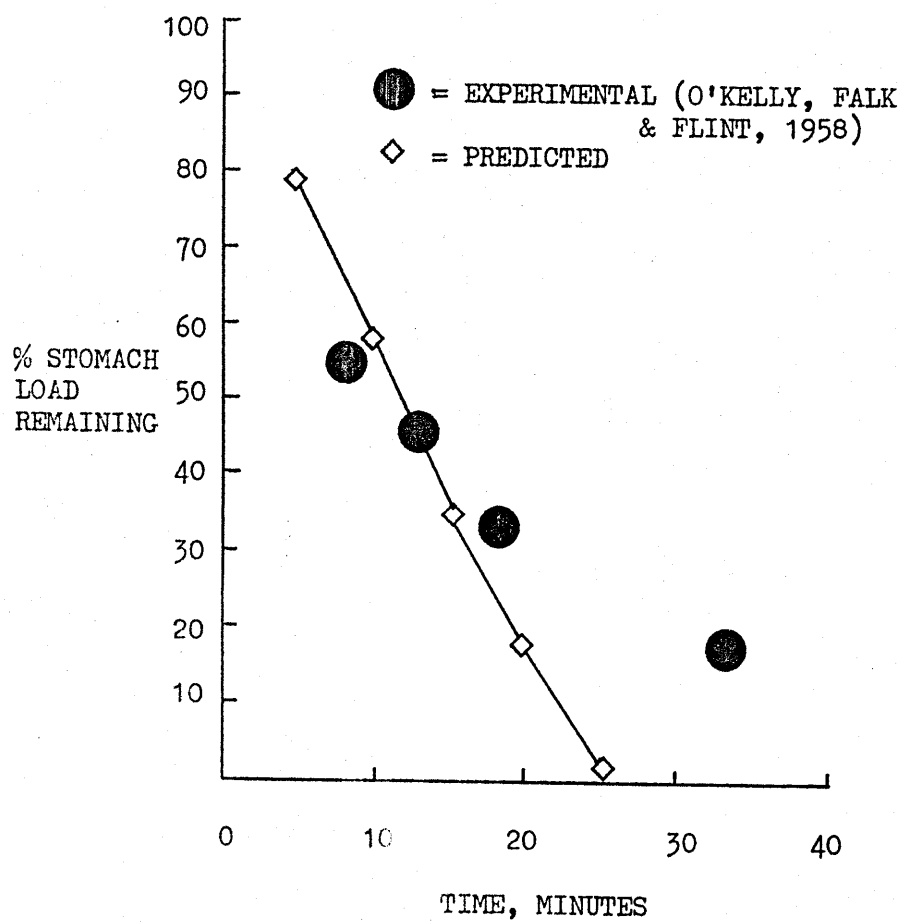


FIGURE 8.2- STOMACH CLEARANCE OF 3%  
BODY WEIGHT WATER LOAD,  
INFUSED AT  $t=0$ .

Validation of the Stomach System

O'Kelly, Falk and Flint (1958) investigated the rate at which water and solutions were both cleared from the stomach, and absorbed from the intestine. These authors found that clearance of a 9 ml water load from the stomach followed a 'negative growth function'. Their results are shown in Figure 8.2. The predicted figures from the simulation are also shown. It can be seen that generally there is a reasonable fit. Data on the experimental errors are unfortunately not available.

This system is further validated by some of the simulations presented in Chapter 14.

Intestine SystemIntroduction

The main aim of the alimentary tract is to ensure a continual supply of water, electrolytes and nutrients. This necessitates coordination of food movement, (aided greatly by the stomach), the secretion of digestive juices and absorption of the end-products of digestion.

In this simulation, the overall behaviour of the intestine is greatly simplified. It has been found however that the system presented is sufficiently realistic for current purposes.

Intestine- DescriptionFood Digestion

The essential question here is- how long does food take to disappear from the intestine? Based upon data from rats, Toates (1971) p.217, used the function;

$$f = 0.016 * if$$

where  $f$  = rate of absorption (g/minute)

$if$  = intestinal food (g)

Whilst this may be a useful general rule, there appear to be many complicating factors. For example, Booth and Jarman (1976) showed diurnal variation in food digestibility. Thus a 1g load of glucose took about 3 hours to be absorbed during the day, but only 2 hours at night. Suda and Saito (1975) showed that the rhythmic changes in digestive activity are in phase with the feeding pattern, even in rats trained to eat during the light period. In

addition, Armstrong, Clarke and Coleman (1978) noted that during the dark period, the small intestine appeared much pinker in colour, with more visceral bleeding. This they attribute to variations in digestive and absorptive capacities of the intestine at different times of the day. Following study of the data presented by Armstrong, Clarke and Coleman (1978), it was decided to represent digestion of food constituents as being a square root function of intestinal content. This, it was felt, provided a better fit to the published data. With other techniques, it was frequently difficult to avoid occasions when the intestine was empty, let alone ensure relative constancy of gut contents, as appears to be the case (Armstrong, Clarke and Coleman, 1978).

One potential complicating factor not incorporated in the current simulation is the interesting finding of Wiepkema, Prins and Steffens (1972). They showed that new food being eaten by the rat reaches the intestine very rapidly, even when the stomach is already full of old food. The manner in which this is accomplished is unclear, but its relevance is obvious. Within a few minutes of the start of a meal, derivatives of the ingested food may reach receptors in the upper intestine, informing the animal about the nutritive value of the recently ingested food. This may serve to corroborate information already provided by receptors in the stomach, known to signal food satiation (Deutsch, 1978).

During the course of a normal day, the nutritive state of a small animal such as the rat may vary considerably.

This raises the question as to whether such variations can impair the ability of the intestine to digest and absorb nutrients. Whilst long-term food deprivation will undoubtedly affect intestinal performance, (e.g. Jackson, 1925), semi-starvation appears to have relatively few effects (Williams and Senior, 1978; Groseclose and Hopfer, 1978; McNurlan, Tomkins and Garlick, 1979).

The intestine system is shown in Figure 8.3.

Block 1 calculates net carbohydrate flow in or out of the intestine. CAS4 represents the carbohydrate flow from the stomach, whilst FAIG represents the rate of digestion, in g/s. Delivery of material to the intestine is entirely from the stomach; no regard is given to endogenous matter, as this ultimately represents no net energy gain or loss to the animal. Block 2 multiplies the net flow by .99. This represents the proportion of available carbohydrate successfully digested under normal circumstances (the conversion efficiency). Block 3 then integrates this signal to give (approximately, considering block 2) the amount of carbohydrate present in the gut at any one time (CAI3). Perhaps more specifically, it should be described as the amount of carbohydrate available for digestion, in g. Block 4 calculates the 'concentration' of carbohydrate relative to total intestine contents (fluid and solid). Blocks 5 and 6 then apply to this signal a variable representing diurnal variations in digestive ability. Day-time performance is assessed as being two-thirds of night-time digestive ability (Booth and Jarman, 1976). The final rate of material loss from the stomach is derived by blocks 7 and 8, which apply a

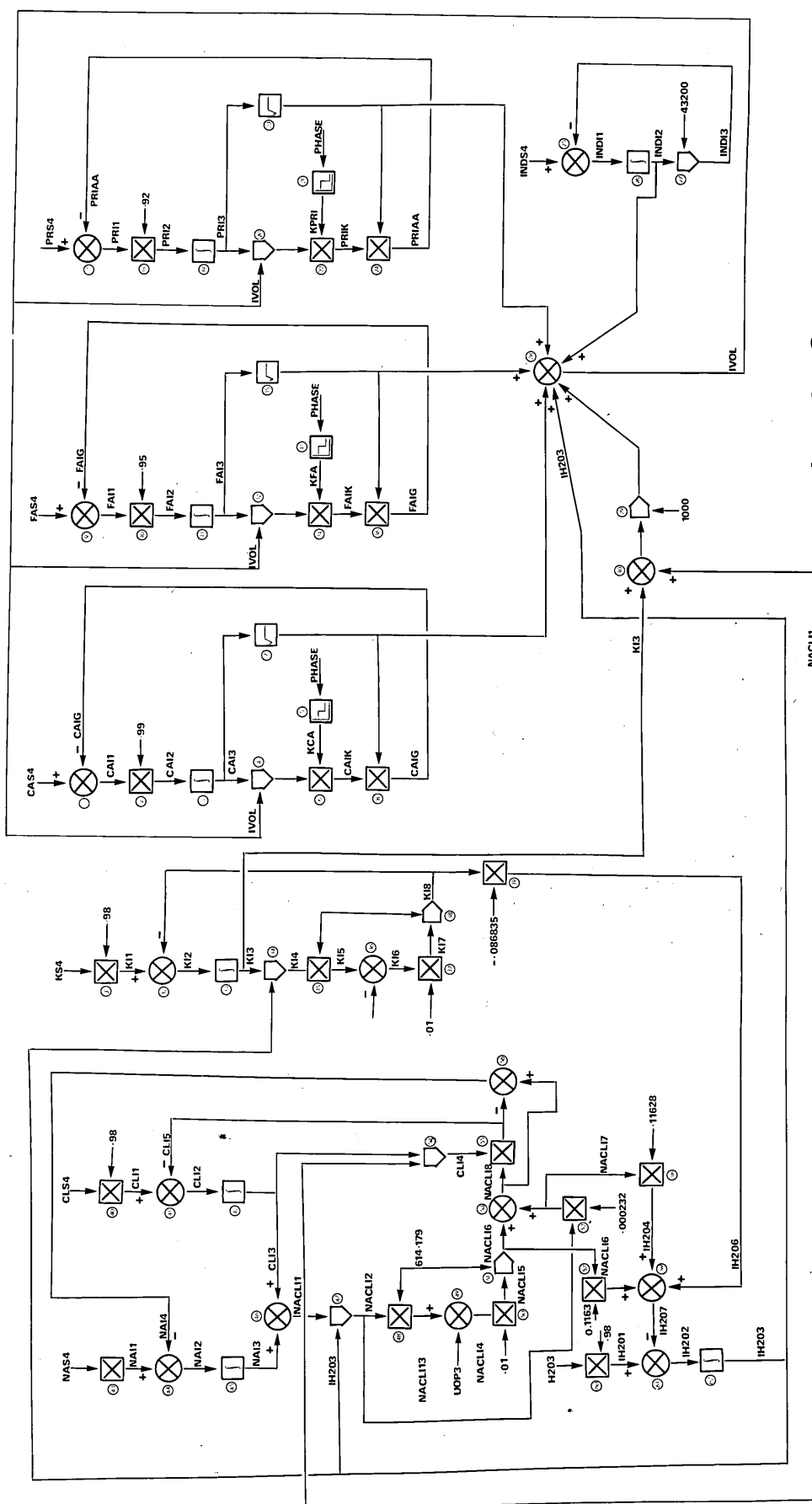


FIGURE 8.3



variable proportional to the square root of gut carbohydrate contents.

Similar systems are used for assessing intestinal turnover of the other digestible food constituents, i.e. fat and protein. Thus in order to understand the mode of action of any system in blocks 9 to 24 it is only necessary to examine the description of the corresponding system in blocks 1 to 8 above.

Indigestible material is dealt with somewhat more simply. The only means by which this material can be lost is via the faeces. Consequently the system in blocks 25 to 27 simulates this by means of an exponential delay. Block 25 subtracts faecal loss of indigestible material from stomach delivery rate to give net loss or gain to or from the intestine. Block 26 then integrates this to give total intestine content of indigestible material at any one time. Faecal loss is assumed to be approximately proportional to intestine content, so block 27 divides this content by a constant, giving faecal loss rate.

Block 28 calculates the sum of all matter in the intestine, including liquid and electrolytes (appropriately corrected for unit in block 29).

#### Electrolyte and Water Transfer

Electrolyte shifts across the intestine wall can be either passive, i.e. down a concentration gradient, or active, i.e. energy assisted, and usually against a concentration gradient. As with the description of the stomach system, the intestinal turnover of Potassium shall

be dealt with first.

### Potassium

This system is somewhat simplified, as it does not at present permit active transport of Potassium. There is a well-controlled hormonal system determining extra-renal Potassium homeostasis, and it appears that aldosterone and insulin may well play a role in determining active transport of Potassium across the cell wall (Guyton, 1976, p.1022; Bia and Defronzo, 1981). Incorporation of this is planned for the future; currently the gain to the current topic may not justify the effort of incorporating what may well turn out to be a very complex system.

Blocks 30 to 38 comprise the intestinal Potassium system. Block 30 reduces the stomach delivery rate of Potassium to simulate the influence of normal faecal loss, as in the intestinal food systems. Block 31 then derives net flow into or out of the intestine, and block 32 integrates this signal to give the intestinal Potassium content. This, when divided by the volume of intestinal water in block 33, gives the Potassium concentration. Note that there is no restriction on the release of Potassium (or any other electrolyte) to intestinal fluid, as in the stomach system. It is here assumed that digestion has generally proceeded to the point where all the intracellular contents of the food have been released from their confines. This additional release of electrolyte may explain the observation of Toates (1971), p.217, that the ratio of water to food is higher in the intestine (about 1.3 to 1) than in the stomach (about 1

to 1).

Block 34 converts the intestinal Potassium concentration to the appropriate osmotic pressure. Blocks 37 and 38 then deduce the osmotic pressure gradient, and the consequent flow of Potassium ions across the intestine wall. Ions leaving the intestine by this route become part of the vascular pool. Block 38 calculates the flow of water that occurs as a consequence of Potassium transfer.

#### Sodium and Chloride ions

The systems subserving the intestinal turnover of Sodium and Chloride ions are very similar, and are to an extent inter-related, as in the stomach. In this case however, a form of active transport is incorporated, to ensure that the intestine system generally did not simply come to a passive equilibrium with the vascular compartment. This is as found in real animals (Guyton, 1976).

Blocks 34 and 37 respectively calculate the proportions of Sodium and Chloride ions normally lost via the faeces. Blocks 35 and 38 then derive net flows to or from the intestine. These signals are then integrated in blocks 36 and 39 to give total intestinal content of Sodium and Chloride ions respectively.

Blocks 40 to 50 are responsible for calculating active and passive shifts of both Sodium and Chloride ions. Block 40 sums intestinal Sodium and Chloride ions, and Block 41 divides this by intestinal water to give the concentration. Blocks 42 to 45 then derive the concentration gradient across the intestine wall, and hence passive transfer of

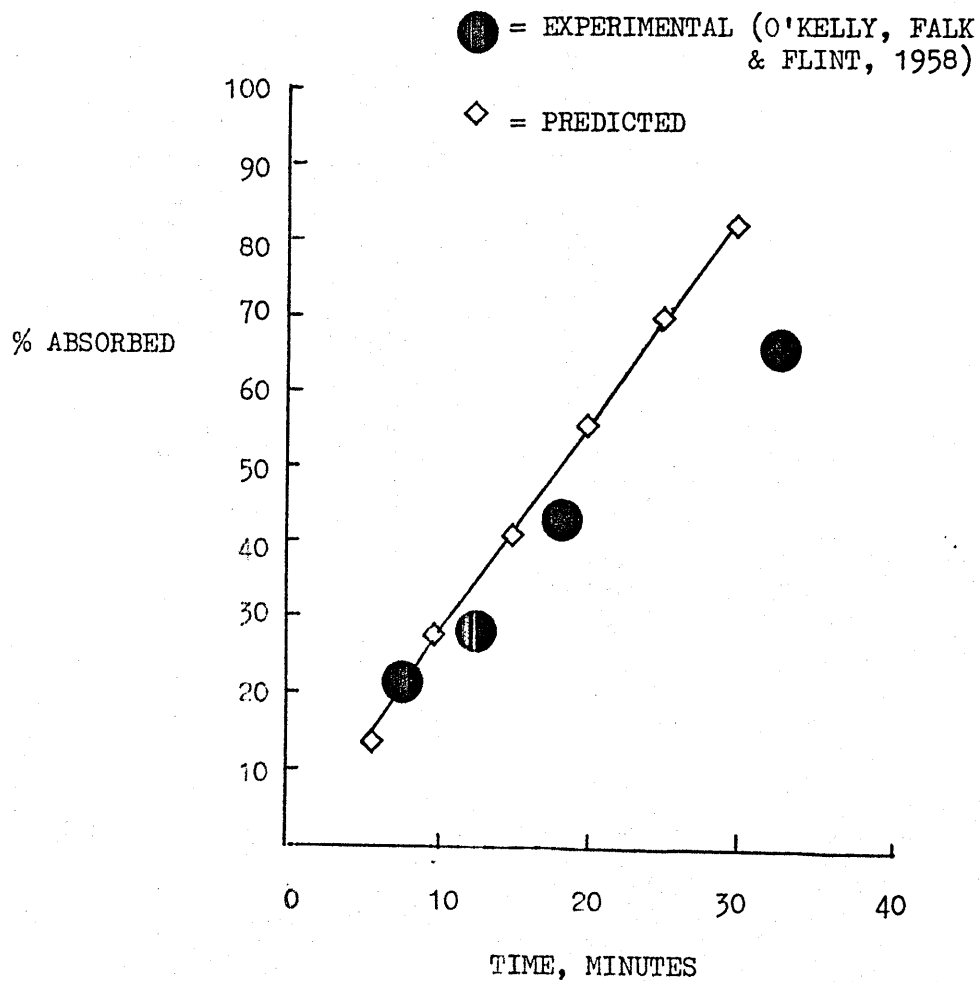


FIGURE 8.4- INTESTINE ABSORPTION OF A  
3% BODY WEIGHT WATER LOAD, INFUSED  
INTO THE STOMACH AT  $t=0$ .

both Sodium and Chloride. Block 46 calculates active transport, assuming it to be directly proportional to intestinal Sodium and Chloride content. Block 47 sums active and passive transport, whilst blocks 48 to 50 apportion the total electrolyte transfer between Sodium and Chloride.

### Water Turnover

Intestinal water transport can occur either by passive flow, down a concentration gradient, or as a consequence of active Sodium or Chloride transport.

Block 54 performs the usual function of simulating faecal loss, reducing stomach supply of fluid by the requisite proportion. Block 55 then calculates net fluid flow. Blocks 51 and 52 convert shifts of Sodium and Chloride to the appropriate fluid shift, whilst block 53 sums all electrolyte-induced movements to give total transfer. Finally, block 56 integrates net flow to give intestine fluid content.

### Validation of the Intestine System

Once again, the data of O'Kelly, Falk and Flint (1958) are used for validation. Their results, illustrating the absorption from the intestine of a 9ml stomach load are shown in Figure 8.4. The predicted data is also shown, for comparison. Whilst predicted absorption is rather more rapid than the experiment would suggest, the agreement is still reasonable. This is particularly true, considering that this simulation is also a test of the stomach system; intestinal

absorption is presumably also a function of delivery rate by the stomach.

Energy Metabolism

The system presented here (see Figure 8.5) is essentially a 'metabolisable energy' model. Thus one will not find, for example, a representation of the effects of a particular amino acid deficiency; such studies are beyond the scope of the current project. The description of the animal's overall energy state permits an analysis of the fate of intracellular fluid, and this is of greatest relevance. Thus representation in any greater depth is currently unnecessary.

As discussed in earlier sections, ingested food is regarded as consisting of four 'dry matter' components (excluding electrolytes). These are protein, fat, carbohydrate and indigestible matter. All but the latter contribute in varying degrees to the energy balance of the animal.

In protein digestion, pepsin and proteolytic enzymes (secreted by the pancreas) break protein down into peptide fragments. As such, the body is still incapable of absorbing them, so the fragments are broken down further to free amino acids by carboxypeptidase (also from the pancreas) and aminopeptidase (from the intestinal lining). These free amino acids are then actively transported by a variety of techniques across the intestine wall (Guyton 1976, p.884). This process results in the release of energy, much of which can be utilised by the animal. The theoretical maximum, determined by the heat of combustion less energy lost in the urine (primarily urea), is around 18.1 KJ/g, or 4.1 Kcal/g.

However, the transfer of energy within the animal is not as efficient as this; approximately 25% is wasted as heat (Davidson, Passmore, Brock and Truswell, 1975). For want of information, this conversion efficiency of 75% (derived empirically) is assumed to apply to all energy-providing food constituents.

Most fats ingested are triglycerides, with smaller proportions of cholesterol and phospholipids. The main problem with fat digestion is that fats are not water soluble, whereas the enzymes capable of breaking them down are. This is overcome by the liver's secretion of bile salts, which emulsify the fats and thus increase the surface area accessible to the enzyme lipase. The digestion products eventually form droplets (micelles), which can then be transported across the intestine wall. Fat is particularly energy-rich; conversion efficiency in the gut is high (around 95%, compared with 92% for protein), and each gram of fat can produce up to 39 KJ, or 9.37 Kcal (Guyton, 1976).

Carbohydrates form the largest digestible fraction of most foods laboratory rats are likely to receive. The predominant carbohydrate is starch. This is first broken down to form disaccharides in the stomach and intestine (the saliva of rats contains large amounts of amylase, the active enzyme). Further enzymes in the intestinal lining break the disaccharides into the monosaccharides glucose, galactose and fructose. Digestion of carbohydrates and the subsequent transport of derivatives across the intestine wall is rapid, and conversion efficiency in the gut is very high- around 99%. The heat of combustion of carbohydrates is less than



any other energy-producing food component (around 4 Kcal/g).

Blocks 1 to 3 (see Figure 8.5) convert the flow of nutrients arising from digestion of carbohydrate, fat and protein into their respective energy contributions to body energy needs. CAIG represents the rate at which carbohydrates are digested by the intestine; FAIG and PRIAA are the corresponding values for fat and protein, respectively. All these rates of uptake are expressed in mg/s. Block 4 sums these contributions, and block 5 applies the conversion efficiency of .75. The output of this block represents the energy supply from the gastro-intestinal tract (EIN), in cal/s. Block 6 calculates the animal's rate of energy use, as a function of the phase of day. Estimates of metabolic rate vary somewhat, but generally they are around 40 calories/minute for a 300g rat (e.g. Morrison, 1968; Booth, Toates and Platt, 1976). LeMagen's (1981) estimates of 45 cal/min at night (the active period) and 40 cal/min during the day appear representative, so are the values employed here.

Block 7 subtracts metabolic rate (MR) from energy supply (EIN) to give the net energy supply (EIN1). Basically, an energy excess will then expand energy reserves, whilst a deficit will deplete them.

By several processes, the metabolism of food products at the cellular level yields water, which is then available for the animal's utilisation (Bintz, Palmer, Mackin and Blantin 1979). This source of fluid can be of great benefit during water deprivation; indeed, some desert rodents are so efficient in their economy of water that their metabolic

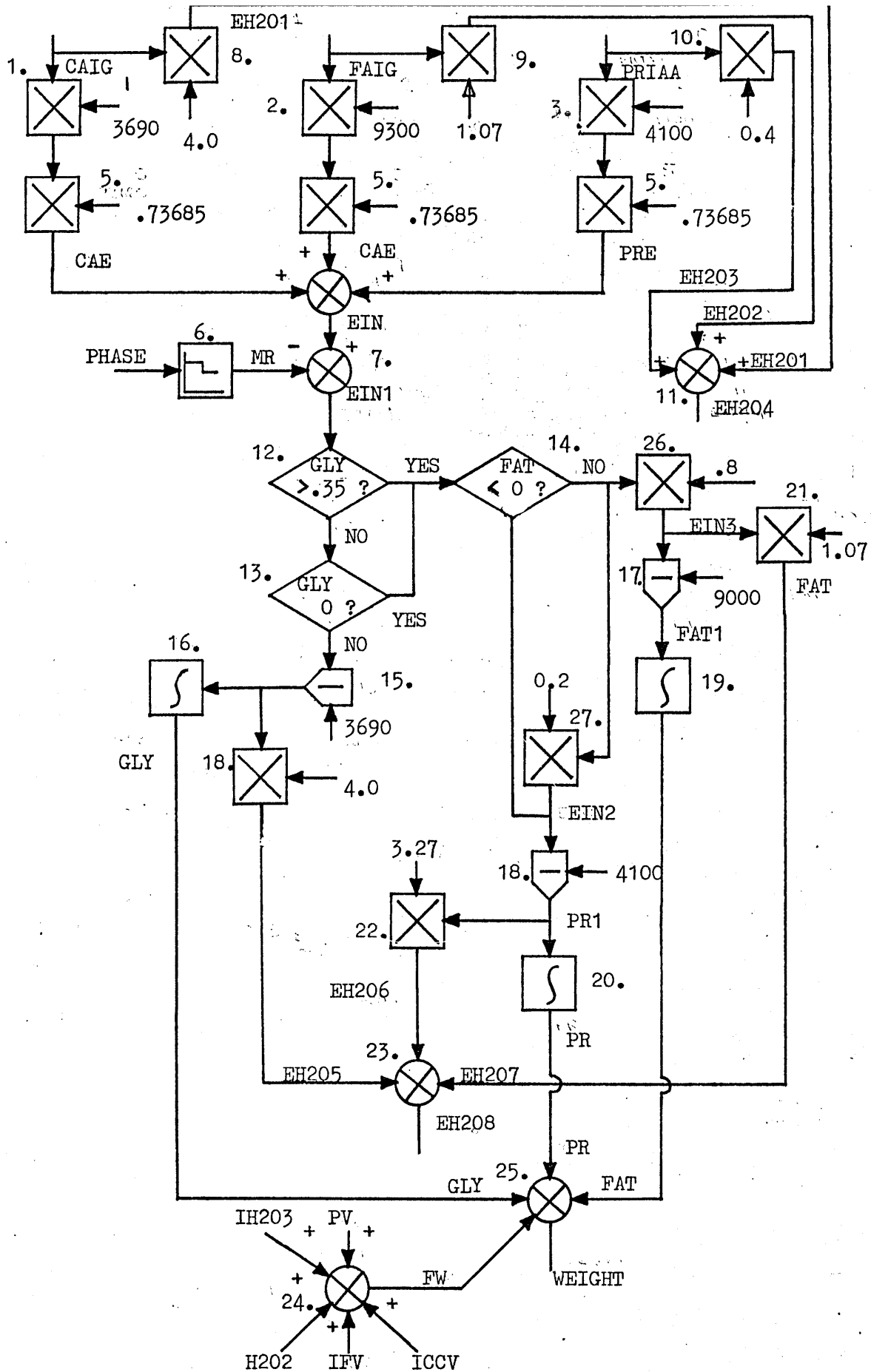


FIGURE 8.5- ENERGY SYSTEM.

water is adequate for all needs (Schmidt-Nielsen, 1964).

The water contributed by any energy store as a consequence of its depletion may be considered as having two components. First, there is water released as a by-product of the oxidative processes involved. Second, there is the release of 'bound' water, associated with the energy store within the cell, and released in proportion to the store's depletion.

During starvation and water deprivation, an animal must rely upon body resources for water and energy. Water is made available as a consequence of release of preformed water contained in tissues, and by oxidation of hydrogen in energy reserves. The proportions of contained and oxidative water yielded by differing types of tissue vary greatly. Thus for each gram oxidised, fat yields 1.07 ml of water (Peters and Van Slyke, 1946; Davidson, Passmore et al, 1975, p.95); however, adipose tissue contains very little preformed water (Bintz and Mackin, 1980). Protein yields very little oxidative water- only 0.4g per g of protein (Peters and Van Slyke, 1946; Davidson, Passmore et al, 1975, p.95), but contains relatively large amounts of preformed water. However, the sum of preformed water and water of oxidation from fat still exceeds that available from protein (Bintz and Mackin, 1980). Thus it may appear that that a starving and water-deprived animal would do well to meet its energy needs by metabolising fat, as this would then also contribute most to water requirements. Unfortunately, this turns out not to be the case. The oxidation of 1 g of fat requires 2.01 l of Oxygen, whereas protein only needs .97 l

Oxygen/g (Schmidt-Nielsen and Schmidt-Nielsen, 1951). The functional significance of this is that the additional Oxygen required necessitates an increase in respiration, and hence a proportionate increase in pulmonary insensible water loss. Unless the animal concerned is capable of restricting this loss, then the oxidation of body fat reserves will result in a net loss of water. There are means by which PIWL can be reduced. For example, hibernating and desert animals frequently live in deep burrows, in which humidity can be kept at a high level. The high humidity of inhaled air consequently reduces the rate at which water evaporates from pulmonary surfaces (Schmidt-Nielsen and Schmidt-Nielsen, 1950). This permits the almost exclusive oxidation of fat to fulfil energy requirements (Kayser, 1950).

Under normal circumstances however, such behavioural adaptations are not available to the rat. Thus exclusive utilisation of fat is not feasible during food and water deprivation; presumably during food deprivation with water available, the story may be somewhat different, as this would permit fat utilisation. The situation is summarised below. The data presented is from Bintz and Mackin (1980), following their studies of Richardson's ground squirrels. Applicability to rats is assumed here.

	Oxidative Water	Bound Water	Necessary PIWL	Net Loss/Gain
Fat	1.07	.04	2.45	-1.34
Protein	0.4	2.87	1.18	+1.57 *

\* This includes the urinary loss of .52ml/g, for excretion of protein nitrogen.

Unfortunately, it has not been possible to deduce such complete figures for the body store of glycogen, which acts as a short-term energy supply. However, it has been shown that 1g of carbohydrate (of which group glycogen is a member) can yield 0.6 ml of oxidative water (Davidson, Passmore et al, 1975, p.95). In addition, each gram of glycogen binds between three and four ml of water, which is freed and excreted in the urine as the glycogen store is depleted (Davidson, Passmore et al, 1975, p.297; Garrow, 1974).

Bintz and Riedesel (1967) showed that starved and water-deprived rats became dehydrated; on the other hand, rodents that were more efficient in their water metabolism (e.g. ground squirrels) maintained water balance. Nevertheless, it must be assumed that the oxidation of energy resources contributes significantly to meeting a rat's water requirements during food and water deprivation, and that this factor should be incorporated in a simulation of body water metabolism.

The oxidative water yields that accrue from fat, carbohydrate or protein are assumed to be the same whether from food in the gastro-intestinal tract or from body reserves. However, digested food is likely to be re-assimilated, to form part of the body energy stores. This will require the deposition of water, (both physically and chemically bound), so there can be no net gain of water, at least in the rat. In addition, the amount of 'bound' water from digested food will not normally be the same as the figures given above. Instead, it will presumably correspond

to the 'water content' given in the food's assay. Thus laboratory rat food will have a water content of about 6 per cent (see earlier). The dietary intake of this food component is determined by the stomach system, using variable FH20IN. Thus block 8 (Figure 8.5) derives the production rate of oxidative water from carbohydrate digestion (EH201, ml/s). Blocks 9 and 10 perform similar tasks for fat and protein (EH202 and EH203) respectively. The constants used are from Bintz and Mackin (1980), as discussed above. Block 11 sums these influences, to give total digestive oxidative water production rate (EH204, ml/s).

The movements of oxidative and bound water related to variations in body energy stores are represented by blocks 17, and 21 to 23. Block 13 derives the water flow as a consequence of glycogen deposition or utilisation; blocks 21 and 22 do likewise for protein and fat respectively.

Most of the body's responses to energy deficits (usually as a result of food deprivation) relate directly to the brain's sensitivity to drops in energy supply. It is essential that blood glucose levels be maintained at concentrations in excess of 60 mg/100 ml (Guyton, 1976). Below this level, the brain's glucose supply may become inadequate, resulting in coma and death. The situation is further complicated by the fact that under normal circumstances, glucose is the only energy substrate acceptable to the brain. Only following severe starvation does the brain begin to adapt to utilising fatty acids. Therefore it is essential that the body maintain a reserve

of energy, to tide it over not only prolonged periods of deprivation, but even between meals.

The body's energy stores consist, for the purposes of this simulation, of three compartments; glycogen, fat and protein.

Glycogen, stored mostly in the liver, acts as the body's first line of defence against low plasma glucose levels (hypoglycaemia). This short-term supply is usually enough to last for a few hours only. Thus it is mainly used to tide the animal over inter-meal intervals, and during periods of rest. Parrilla (1978) studied the physiological responses of rats to six days of starvation. Within the first day, hepatic glycogen was depleted and fat, the second body energy store, mobilised. Not all rodents respond in this manner; there are considerable species, as well as individual differences. Thus the Golden Hamster (*Mesocricetus auratus*) appears to be debilitated by fasts of only 12 hours, which can produce weight losses of up to 20% (Borer, Rowland, Mirow et al, 1979). Such responses presumably relate to the normal eating pattern of the animal, and the size of its energy stores. Rixon and Stevenson (1957) have shown that the survival time for starved rats is related to the proportionate body weight loss per day of starvation, not the initial body weight. An individual's survival time could be predicted from its metabolic rate. Previous diet had little effect on survival time.

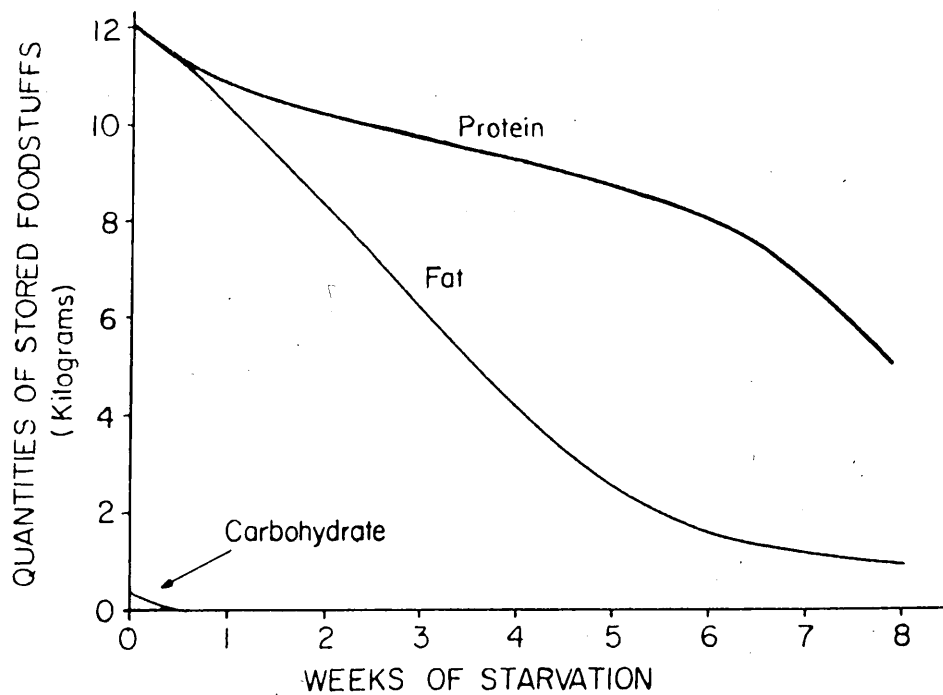
It should perhaps be noted that during periods of energy deficit the body also takes steps to reduce its

energy needs. This 'glucose sparing' ultimately frees more glucose for use by the brain. Such a system of glucose sparing is not represented in this simulation although, in a crude form, it is in the smaller simulation described earlier.

As mentioned above, body fat reserves are mobilised following glycogen depletion. While these last, they are preferentially depleted relative to the third body energy store; protein (see Figure 8.5). Such, at least, is the traditional view. Parrilla (1978) noted that from day two of starvation, his rats demonstrated a gradual increase in urinary nitrogen. Thus he concluded that rats do not spare body protein during starvation, probably because the glycogen and fat stores are used up so quickly. It is considered that this is something of a simplification, however. Even Figure 8.6, representing human responses to starvation, shows some depletion of body protein whilst fat reserves are still plentiful.

Normal energy store sizes are difficult to assess. However, good estimates are available for liver glycogen, with most authors (e.g. Fuller and Diller, 1970; Gagliardino, Pessacq et al, 1978; LeMagen and Devos, 1980) concluding a peak value of about 350 mg, in a rat of about 300g. Estimates for the other stores are much more arbitrary, and can only be roughly assessed according to the rate at which energy is used during periods of deprivation, and survival times. Parrilla (1978) showed a significant rise in urinary Nitrogen after two days of starvation. Consequently it is assumed that readily mobilised fat stores





**Body food stores in starvation**

FIGURE 8.6  
FROM GUYTON (1976)

contain enough energy to last for one day (54 Kcal at a metabolic rate of 40 cal/minute). At an energy density of 9 Kcal/g, a fat store of approximately 6 g is indicated. An assumption made here is that fat is used preferentially to protein, so that for every 1 g of protein lost during starvation, 4 g of fat are mobilised. These ratios are derived from Figure 8.6 (from Guyton, 1971).

Blocks 12 to 14 demonstrate the partition of energy supplies and demands between the three energy compartments. Block 15 converts the rate of energy shift (either supply or demand) into the rate of change in glycogen stores, and block 16 integrates it to give total body glycogen (GLY). Block 18 converts the rate of glycogen change to the associated flow rate of water (both free and oxidative).

Fat and protein stores are called upon when glycogen stores are already depleted, as shown in block 14. Blocks 26 and 27 apportion the energy demand between fat and protein in the ratio of four to one as discussed above. Should even fat reserves be depleted however, the entire burden of maintaining an adequate energy supply falls on to protein. That such a situation can occur is illustrated in Figure 8.6. The remaining blocks perform analogous operations to those already described for glycogen. Thus blocks 17 and 18 convert energy demands to net transfer of fat and protein reserves respectively. Blocks 19 and 20 integrate these signals to give total reserves, and blocks 21 and 22 calculate associated water flows. Block 23 sums the three flows of water associated with body reserves.

Blocks 24 and 25 then sum all body components, to give

an estimate of body weight (excluding gastro-intestinal contents).

It must be conceded that the energy metabolism system described here is somewhat crude, and probably mistaken in some of the assumptions made. However, if this model can at least demonstrate that the energy status of an animal is a major determinant of its drinking responses during repletion, then its most important aim will have been achieved. To date, this aspect has received scant attention, and it is felt that a closer examination of the interactions between energy and fluid balance could help resolve many of the current paradoxes.

Certainly, the model could be greatly improved. For example, Garrow (1974) showed that in early days on a reducing diet (man), there is a rapid glycogen and protein loss, rather than glycogen alone. Once the glycogen stores are depleted (which does not take long), the rate of protein breakdown also reduces greatly. This reduction, Garrow (1974) suggests, is due to signals indicating glycogen depletion. These signals reduce protein turnover, and hence urinary Potassium.

An additional phenomenon that could fruitfully be investigated is described by Davidson, Passmore et al (1975). In post-operative (gastrectomy) food deprivation (humans), much of the water lost is intracellular, and is thus accompanied by a Potassium diuresis. This has been attributed to the stress of the operation. In simple starvation however, the ratio of urinary Potassium to Sodium is much lower, indicating that most of the water lost is

extracellular in origin (Porter and Knight, 1970).

Validation of the Energy System

No independent validation is offered here, as it has proven difficult to obtain sufficiently independent data for comparison with predicted results.

CHAPTER 9The Renal and Insensible Water Loss SystemsThe Renal SystemGlomerular FiltrationIntroduction

Most of this sub-system is concerned with calculating the various components of net ultrafiltration pressure, PUF. These components are glomerular capillary pressure, which tends to increase glomerular filtration rate, and tubular pressure and plasma colloid osmotic pressure, both of which tend to reduce glomerular filtration.

The model described here represents a single nephron of a rat kidney.

Brenner, Deen and Robertson (1976) showed that

$$J_v = K ((P_{GC} - P_T) - (P_{COP} - P_{FCOP}))$$

where  $J_v$  = glomerular filtration rate at any point

$K$  = capillary permeability coefficient

$P_{GC}$  = glomerular capillary hydrostatic pressure

$P_T$  = tubular pressure

$P_{COP}$  = glomerular capillary colloid osmotic pressure

$P_{FCOP}$  = tubular fluid colloid osmotic pressure

This represents a type of Starling's equilibrium, first used to explain the balance of hydrostatic and osmotic forces that determine net fluid flow across the capillaries between vascular and interstitial compartments (Starling, 1896).

Under normal circumstances, the protein content of glomerular filtrate is very low (Gaizutis et al, 1972), so one can safely assume that for our purposes  $TFCOP = 0$ .

This function gives glomerular filtration at a particular point. Thus to know the total filtration rate for an entire glomerulus, it is necessary to calculate the mean values of  $PGC$ ,  $PT$ , and  $PCOP$ . In practice, the only variable to alter significantly between afferent and efferent ends of the glomerular capillary is plasma colloid osmotic pressure, due to loss of plasma to the Bowman's capsule without a corresponding loss of plasma protein. Thus in the model presented here, net ultrafiltration pressure is calculated for afferent and efferent ends of the glomerular capillary, and the mean ultrafiltration pressure derived from the sum of these two. Actual glomerular filtration rate is in turn derived from the mean ultrafiltration pressure,  $PUF$ .

### System Description

Blocks 1- 5 (see Figure 9.1) calculate single nephron glomerular blood flow and pressure in the glomerular capillaries, as a function of arterio-venous pressure gradient, and glomerular resistance.

The arterio-venous pressure gradient is normally about 115 mmHg, i.e. slightly less than arterial pressure (see vascular compartment). Thus a total nephron resistance of 57.59 would predict a single nephron glomerular blood flow (SNGBF) of approximately 2.0 nl/s. This is in agreement with a range of experimentally observed values. Brenner et al (1972) give a mean SNGBF of about 2.06 nl/s. It should be

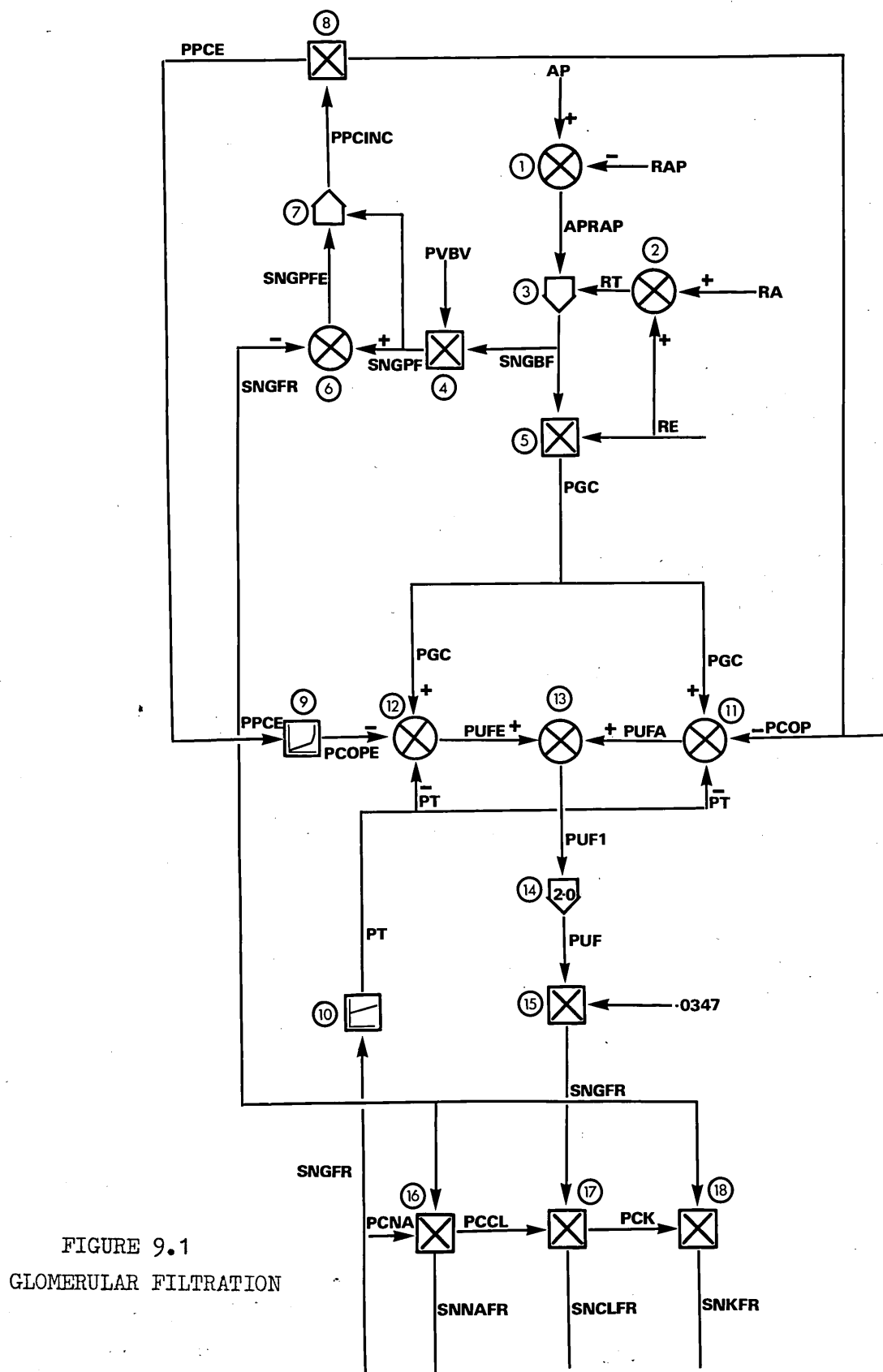


FIGURE 9.1  
GLOMERULAR FILTRATION

pointed out, however, that this mean figure makes allowance for a lower efferent glomerular blood flow due to glomerular filtration. Afferent SNGBF is about 2.23 nl/s.

Block 5 converts SNGBF to SN plasma flow, the predicted value of which is about 1.25 nl/s. Analysis of the data presented by Brenner et al (1972) gives an SNGPF of about 1.04 nl/s. Deen et al (1973), studying the same colony of mutant Munich-Wistar rats (mutant to the extent that they have superficial glomeruli, enabling their study), report an SNGPF of 3.3 nl/s. However, they achieve this high rate by an infusion of 5% body weight of plasma, and omit to give any normal values.

There do appear to be considerable individual differences in SNGPF. Arendshorst and Gottschalk (1980) studied two separate colonies of mutant Munich-Wistar rats and found significant differences in SNGPF. In one colony, SNGPF is 1.67 nl/s; in the other, 2.67 nl/s. However, Robertson, Deen et al (1972) report a normal SNGPF of about 1.33 nl/s, which does tend to substantiate the validity of the predicted value.

Block 5 multiplies efferent glomerular resistance (RE) by SNGBF to give the glomerular capillary pressure, PGC (in mmHg), a determinant of glomerular filtration rate. With an empirically derived value for efferent resistance (RE) of 24.38 mmHg, predicted PGC would be about 48.8 mmHg. This is in close agreement with the reported experimental values of PGC; all are about 45 mmHg. (Blantz, 1974; Brenner, Troy and Daugharty, 1971; Brenner et al, 1972; Arendshorst and Gottschalk, 1974; Brenner et al, 1976). Such apparent



consistency may be misleading, however; all studies cited were of Munich-Wistar rats.

The system in blocks 1 to 5 is an adaptation of that developed by Hall, Coleman et al (1981), following studies of the dog.

Blocks 6 to 9 calculate the glomerular efferent plasma protein concentration, as a function of single nephron plasma flow, filtration rate and normal plasma colloid osmotic pressure. Block 9 converts efferent plasma protein concentration to the appropriate osmotic pressure, using a function derived from Ott (1956). Since single nephron plasma flow (SNGPF) and glomerular filtration rates (SNGFR) are known from experimental studies (see earlier), it is possible to calculate the plasma protein concentration at the efferent end of the glomerulus. It is assumed that none of the plasma proteins find their way into the glomerular filtrate (Gaizutis et al, 1972). Using this technique, (incorporated into this simulation in blocks 6-9), the predicted value of PCOPE is about 37 mmHg, when normal plasma osmotic pressure (PCOP) is 20 mmHg. from Ott (1956). The value of PCOPE predicted by this system is normally about 37.3 mmHg, which is within a few mmHg of the experimental values given by Brenner, Deen et al (1976), (35 mmHg) and Robertson, Deen et al (1972), (35 mmHg approx.)

Block 10 relates tubular pressure (PT) to glomerular filtration rate (SNGFR). This function is based on rat data from Robertson, Deen et al (1972). As a first approximation, the function fitted to the data is a straight line, with an intercept. This intercept may correspond to the pressure

necessary to force fluid through the rest of the kidney tubules. Since other determinants of glomerular filtration are known or can be derived, one can estimate tubular pressure (PT), in mmHg. Thus predicted PT is about 8.7 mmHg, which is in close agreement with the experimental values given by Brenner, Deen and Robertson (1976), of 10 mmHg.

Blocks 11 and 12 calculate the afferent and efferent net ultrafiltration pressures. Blocks 13 and 14 determine the mean ultrafiltration pressure, PUF. Under normal circumstances, the predicted value of PUF (about 6.5 mmHg) is in good agreement with experimental values reported by Brenner, Deen and Robertson (1976) of between 4 and 6 mmHg. However, Arendshorst and Gottschalk (1980) give PUF values of around 15 mmHg, in both colonies of their mutant Munich-Wistar rats. That this figure may be artificially high is indicated by efferent PUF values (PUFE) of around 7 mmHg, suggesting that filtration pressure equilibrium did not occur. In practice, one would expect PUFE to tend towards zero as increased colloid osmotic pressure (PCOPE) reduced effective ultrafiltration pressure.

Block 15 converts mean ultrafiltration pressure to single nephron filtration rate. Published values of the glomerular ultrafiltration coefficient tend to vary somewhat. Arendshorst and Gottschalk (1980), studying Munich-Wistar rats from Brenner's colony reported a filtration coefficient of .066 nl/(s.mmHg), whereas in their own colony of Munich-Wistar rats, it was only .033 nl/(s.mmHg).

The situation was resolved by adopting an alternative technique of calculation, using predicted values of PUF and SNGFR. By this means it was found that the higher value of .066 produced negative values of PUF<sub>E</sub>, whereas values of about .035 nl/(s.mmHg) produced the desired near equilibrium at the efferent end of the glomerulus. Within a large range, it has been shown that the magnitude of the permeability coefficient does not greatly affect filtration rate (Brenner, Deen and Robertson, 1976), so great accuracy is not necessary.

Blocks 16 to 18 calculate the single nephron filtration rates of Sodium, Chloride and Potassium ions.

Block 19 converts SNGFR, nl/s to total glomerular filtration rate, ml/s.

Proximal Tubule SystemIntroduction and System Description

Much of the glomerular filtrate (about 65%; Giebisch and Windhager, 1964) is reabsorbed in the proximal tubules. Solute transport is, for the most part, active. Thus particular characteristics of proximal tubular epithelial cells are the large numbers of mitochondria, to provide the necessary energy, and microvilli, to increase the effective surface area available for solute reabsorption.

The 65% proportion applies to both fluid and most solutes, and so for the purposes of this simulation, fluid leaving the proximal tubule has the same constitution as glomerular filtrate.

This proportion remains much the same in a wide range of physiological circumstances, such as dehydration and hypovolemia. However, the proportion does reduce following infusion of isotonic saline. Such a load of isotonic saline would increase GFR, and thus the flow rate of fluid through the proximal tubule. This lead Gertz, Mangos et al (1965) to suggest that proximal tubular fractional reabsorption was dependent on the passage time of the fluid.

Thus Landwehr, Klose and Giebisch (1967) show that fractional reabsorption in the proximal tubule of an isotonic saline-loaded rat reduces from about 80% to 30%. However, despite an increase in GFR of 46.7%, proximal passage time only reduced by 4.7%. This is by no means large enough to explain the observed reduction in fractional reabsorption. Although it is possible that some of the

decrease may be attributable to the observed increase in tubular diameter, (Gertz, Mangos et al, 1965), as Hayslett et al (1967) point out,

"Sodium excretion in dogs is augmented by saline infusion even when the increment in filtration rate is prevented".

(Hayslett et al, 1967, citing an experiment by De Wardener et al, 1961.)

DeWardener et al (1961) show in a series of cross-perfusion studies that in addition to being independent of GFR, fractional reabsorption is also independent of renal nerve effects, circulating levels of ADH and adrenocortical hormones. Nevertheless, they do "suggest that the saline diuresis is due to the action of a hormonal agent, other than aldosterone, on the tubules".

These suggestions are corroborated by Cortney et al (1965), who showed that intravenous administration of vasopressin and aldosterone had no demonstrable effects on solute or water reabsorption in the proximal tubule. Likewise, Schneider et al (1972) showed that renal arterial infusion of K<sup>+</sup> had no significant effect on fractional or absolute proximal Sodium reabsorption. The only contradictory report is by Gill and Casper (1972), which suggests that renal arterial infusion of norepinephrine increased proximal reabsorption of Sodium.

Thus it is possible that this may be due to hormonal action, but for the purposes of this simulation it seemed

most parsimonious to link proximal reabsorption to haematocrit. As solute transport in the proximal tubules is active, one could expect efficiency to drop if deprived of some of its energy supplies. Certainly, the proximal tubule can with relative ease be irreversibly damaged by relatively short periods of ischaemia. (Lindquist, Chen and Guttman, 1972).

The proximal tubule system used in this simulation is shown in Figure 9.2.

Blocks 1 and 2 calculate the constant for proximal reabsorption, as a function of red blood cell/ plasma ratio. Blocks 3 to 10 calculate the reabsorption rate, and thus proximal efferent flow, of water, (nl/s), Na<sup>+</sup>, Cl<sup>-</sup>, and K<sup>+</sup> (ng/s).

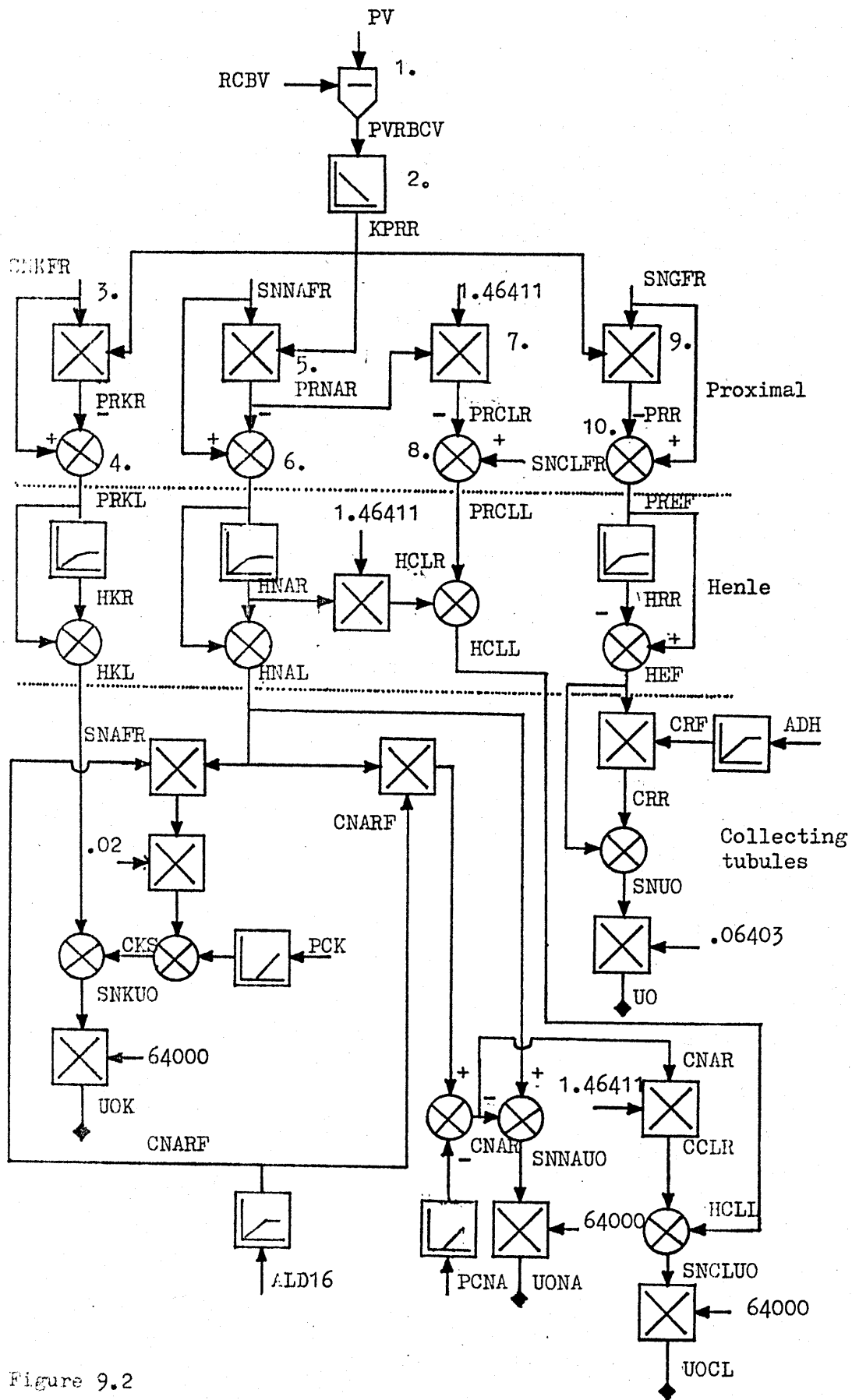


Figure 9.2

Proximal, Henle & Collecting tubules.

Loop of Henle SystemIntroduction and System Description

More specifically, this sub-system represents the thick segment of the loop of Henle, and the first section of the distal tubule. These segments are functionally organised for active transport of Sodium against high concentration and electrical gradients. It is not very permeable to water, and is impermeable to urea.

Schnermann (1968), p.260, showed that the reabsorption rate of water in the loop of Henle was related to the perfusion rate, by the function

$$\text{Reabs. rate} = \text{Perfusion rate} * 0.3 + 5.6,$$

where rates are expressed in nl/min.

However, this particular function only holds true for perfusion rates greater than about 10 nl/min (0.167 nl/s). Normal perfusion rates are about 0.13 nl/s (rat), and an extrapolation of the above function to this normal perfusion rate would predict a reabsorption fraction of about 95%, approximately twice as great as that observed experimentally (Guyton, 1976, p.449).

If one makes the assumptions that

- a) the lower limit of safe extrapolation of Schnermann's (1968) function is about 13.2 nl/min (0.22 nl/s),
- b) normal reabsorption fraction is around 40%, and
- c) the function passes through the origin,

one derives the relationship used.



Using other data provided by Schnermann (1968), it is also possible to derive functions relating perfusion rate of  $\text{Na}^+$  and  $\text{K}^+$  to the respective rates of reabsorption or secretion. Chloride reabsorption is linked to Sodium ion reabsorption.

The control diagram for the loop of Henle subsystem is shown in Figure 9.2.

Blocks 1 to 4 calculate reabsorption, and thus Henle efferent flow of water and Sodium ions. Block 5 calculates the fractional reabsorption of Sodium; blocks 6 and 7 use this to calculate reabsorption and efferent flow of chloride ions. Blocks 8 and 9 calculate  $\text{K}^+$  reabsorption and efferent flow.

Distal and Collecting Tubules

In these tubules, final concentration of the urine is controlled. The collecting tubule epithelia are well designed to resist the extremes of tubular fluid characteristics. The permeability of collecting tubule epithelium to water is determined mainly by the concentration of anti-diuretic hormone, ADH, in the blood.

Anti-Diuretic Hormone Control of Water Absorption

The essential part of this subsystem is a function relating plasma ADH concentration to fractional reabsorption of water. This relationship is derived in the following manner.

Normal daily water flow (in rats) past the loop of Henle appears to be around 321 ml/day, whereas output of urine is around 15 ml/day. (Radford, 1959; Kellogg et al, 1954; Dicker and Nunn, 1957; Collins, 1978). Thus one would predict that with a normal concentration of ADH, the recovery rate would be about 95.3%.

At maximal concentration, urinary output drops to between 10 and 15% of normal, in both laboratory (Dicker and Nunn, 1957) and wild rats (Collins, 1978). This would correspond to a reabsorption fraction of 99.6%, produced by an ADH concentration of about 20 pg/ml (Little and Radford, 1964; Dunn et al, 1973).

On the other hand, is it safe to assume that in the absence of ADH there would be no reabsorption of water in the collecting ducts? Gellai et al (1979) studied the

Brattleboro strain of rat, which has no ADH, i.e. is homozygous for diabetes insipidus. At the start of a water deprivation experiment, urinary output was 90.5 microl/min/100 g b.w. This would give a daily urinary output of 388 ml, which is in reasonable agreement with the estimated Henle efferent water flow of 321 ml/day. Thus it seems safe to assume that all collecting duct reabsorption is under the influence of ADH, i.e. the ADH/ reabsorption fraction function passes through the origin.

#### Aldosterone Control of Inorganic Ion Absorption

These systems work in the same way as the ADH/ reabsorption fraction system. Chloride reabsorption is directly linked to Na<sup>+</sup> reabsorption. In the collecting tubules, Na<sup>+</sup> is exchanged for H<sup>+</sup> and K<sup>+</sup>. (Langley, 1971, p. 560.) Thus, assuming that acid-base balance is maintained, the release of K<sup>+</sup> will be a fixed proportion of Na<sup>+</sup> reabsorption. Calculations showed that this proportion is likely to be around 40% in this particular case, considering the relatively high dietary input of K<sup>+</sup>.

The collecting tubule sub-system is illustrated in Figure 9.2.

Block 1 calculates reabsorption fraction of water in the collecting tubules as a function of plasma ADH concentration, while block 2 converts this fraction to actual reabsorption rate. Block 3 calculates the resulting single nephron urinary output of water, in nl/s. Blocks 4 to 6 treat Sodium in a similar fashion, producing urinary loss in ng/s. Note that the aldosterone 'concentration' used is

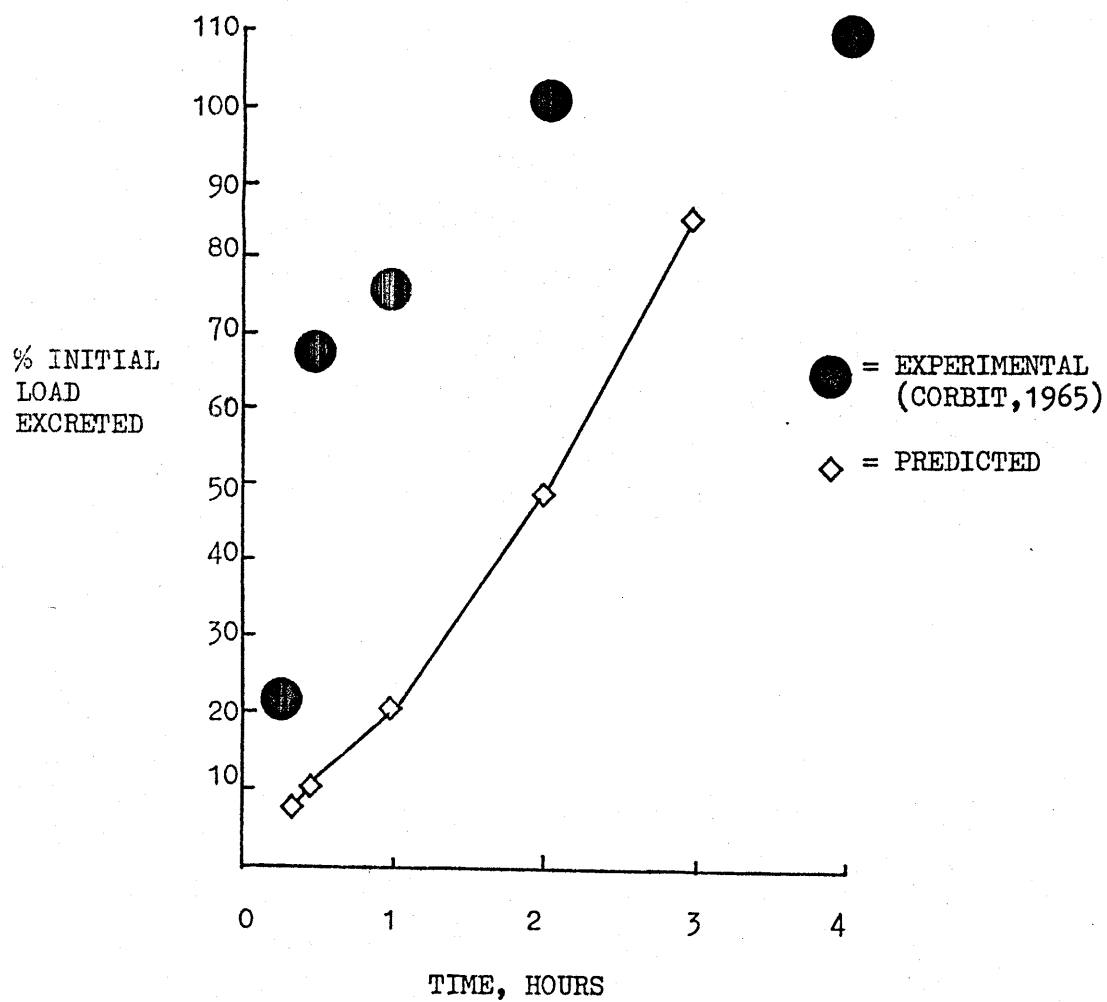


FIGURE 9.3- PROPORTIONAL EXCRETION OF 1ml  
20% NaCl INJECTED INTRAVENOUSLY AT  $t=0$ .

the 'delayed' version, to simulate the time delay that occurs between an increase in aldosterone concentration and its effects on tubular reabsorption. Block 7 produces fractional uptake of chloride ions; this has the same value as fractional Sodium uptake. Block 9 converts  $\text{Na}^+$  reabsorption rate to potassium secretion rate, whilst block 10 calculates single nephron urinary output of potassium.

Finally, blocks 11 to 14 convert single nephron urinary outputs, ng/s and nl/s to overall kidney outputs, mg/s and ml/s.

#### Validation of the Renal System

Cole (1955) and Corbit (1965) studied the renal clearance of an injected load of hypertonic saline. Their data (expressed as a proportion of the total load), is shown in Figure 9.3. Data predicted by the simulation is also shown, for comparison. The simulation appears to show behaviour that lies midway between those of the two experiments cited.

Insensible Water LossIntroduction

Insensible water loss, i.e. evaporative water loss from the skin and lungs, can constitute a large proportion of total water loss from a small animal such as a rat (Dicker and Nunn, 1957.) Rats neither sweat nor pant (or at least very rarely; see Collins and Bradshaw, 1973), and thus cool themselves by spreading saliva on their fur and skin. The importance of saliva for evaporative cooling is strikingly demonstrated by the poor tolerance to heat stress observed in desalivated rats (Hainsworth, 1967.) The ability to withstand extremes of temperature is an important determinant of the geographical distribution of rodent species (Collins, 1978.)

Thus it is not surprising that a positive correlation between salivary insensible water loss (SIWL) and ambient temperature has been observed (Hainsworth, 1967, 1968.) Paradoxically however, although SIWL is behaviourally mediated, there is a minimal level of loss below which the rat will not go. Thus, as Macfarlane and Epstein (1981) point out, neither food nor water deprivation significantly affect SIWL. Even under normal circumstances, SIWL accounts for 30% of all insensible water loss, as shown by Dicker and Nunn (1957), and Ritter and Epstein (1974). It was therefore suggested by Macfarlane and Epstein (1981) that

"rats do not groom less in order to conserve water when in a state of water need. Deprivation of food

or of both food and water reduced insensible water loss by 35- 40%. Since general activity was unaffected by the availability of ingestants, this latter effect appears to be physiologically, rather than behaviourally, mediated."

However, one aspect of SIWL that probably is behaviourally mediated is the variation due to light/ dark phase. This can be very marked (Macfarlane and Epstein, 1981).

Thus, to conclude, SIWL appears to be influenced mainly by ambient temperature and the light/ dark phase. The function relating SIWL to ambient temperature is derived from rat data provided by Hainsworth, (1968).

A second major contribution to overall insensible water loss is made by evaporation of water from the lungs, termed pulmonary insensible water loss (PIWL). The magnitude of this loss is affected by relative humidity (Schmidt-Nielsen and Schmidt-Nielsen 1950), ambient temperature (Hainsworth, 1967,1968; Budgell, 1970), light/ dark phase (Macfarlane and Epstein,1981), fluid deprivation (Dicker and Nunn, 1957; Macfarlane and Epstein 1981) and age (Macfarlane and Epstein, 1981).

The reduction of pulmonary insensible water loss following fluid deprivation appears to be mediated by anti-diuretic hormone (ADH) concentration in the plasma (Dicker and Nunn, 1957; Toates, 1971).

Not all of the influences on PIWL presented above are incorporated in the current model; relative humidity and age

effects are ignored, on the assumption that both would remain relatively constant for the duration of an experiment.

The ambient temperature/ pulmonary water loss function was derived from data by Semple (1950) for the normal temperature range, and Hainsworth (1968) for the higher temperatures.

The relationship between plasma ADH concentration and pulmonary insensible water loss is unfortunately somewhat speculative.

However, according to Macfarlane and Epstein (1981), total insensible water loss reduces by about 40% after 24 hours of water and food deprivation, and remains much the same thereafter. This drop in total IWL can mostly be attributed to a reduction in pulmonary IWL. In addition, as is discussed in the Chapter on ADH control, it has been shown that deprivation periods of this duration produce plasma ADH concentrations of at least 15pg/ml, from a normal value of about 2.5 pg/ml. Thus one can derive a crude, but adequate, relationship. A very similar relationship was developed by Toates (1971), using data given by Dicker and Nunn (1957).

### System Description

The control diagram showing the insensible water loss system is presented in Figure 9.4.

Blocks 1 to 3 calculate salivary IWL as a function of ambient temperature and photoperiod, whilst blocks 4 to 6 perform a similar role for pulmonary IWL. Blocks 7 and 8



# Invisible Water Loss

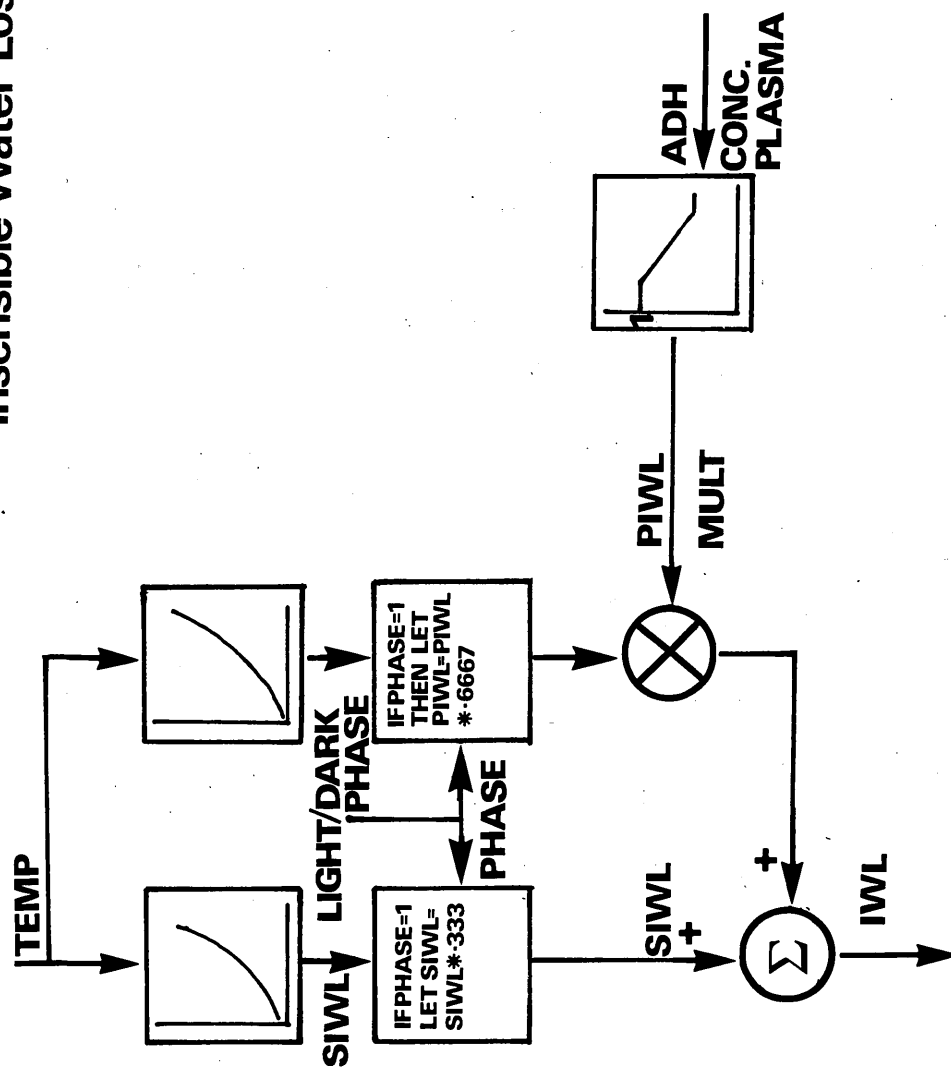


FIGURE 9.4

incorporate the influence of plasma ADH concentration on PIWL, and block 9 summates pulmonary and salivary IWL's, to give total insensible water loss.

Note that faecal water loss, frequently discussed in conjunction with the types of water loss described above, is here dealt with as part of the intestinal sub- system.

#### Validation of the Insensible Water Loss System

Under normal circumstances, the insensible water loss system will predict a daily loss of about 7 ml, which is in good agreement with the published data (see above for references).

CHAPTER 10Renin-Angiotensin System

The system as described here (see Figure 10.1) will be subdivided into two sections. The first, and largest, is devoted to stimuli subserving the release of renin from the kidney, and its subsequent clearance. The remaining section will describe the conversion of renin to angiotensin I, then angiotensin II.

Renin Metabolism

As suggested above, the fundamental causes of renin release are

- a) reduced glomerular filtration rate, b) reduced glomerular pressure, and c) sympathetic stimulation of the kidneys.

It is possible that a) is the underlying cause, with b) and c) both resulting in reduced glomerular filtration (Guyton, 1976, p.469). However, in order to represent the system comprehensively, it is necessary to go to somewhat greater depths. Only in this way will it be possible to examine some of the apparent contradictions observed in current literature. Known influences on renin secretion rate represented here are;

- a) autonomic activity,
- b) right atrial pressure,
- c) renal glomerular pressure,
- d) renal Sodium flow rate,

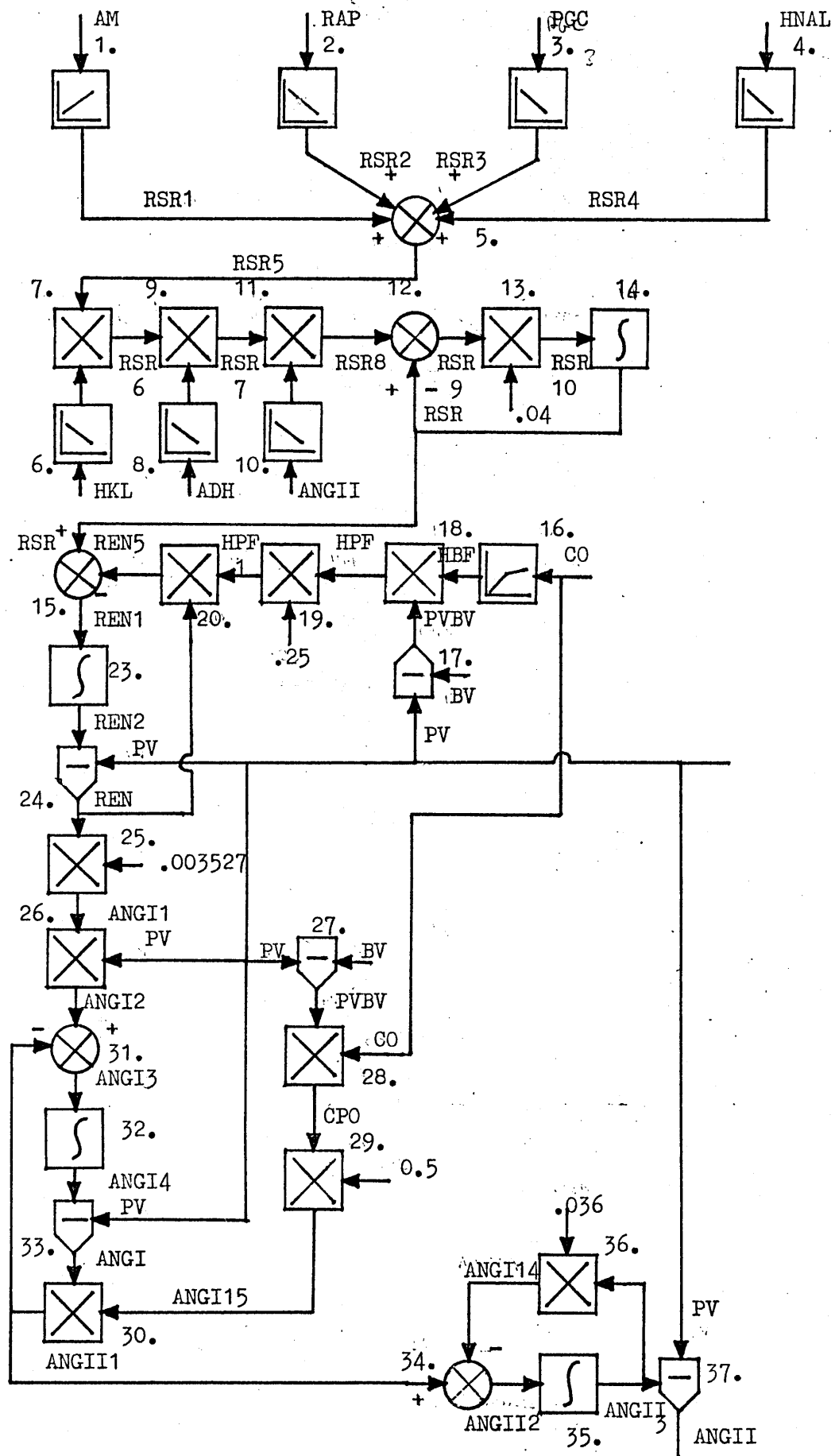


FIGURE 10.1- RENIN- ANGIOTENSIN SYSTEM.

- e)renal Potassium flow rate,
- f)plasma anti-diuretic hormone concentration, and
- g)plasma angiotensin concentration.

Autonomic influence is exerted on the kidney via the vagus nerve; consequently, vagotomy removes this effect (Hodge, Lowe, Vane and Ng, 1969; Gauer, Henry and Behn, 1970; Share and Claybaugh, 1972). In addition, the type of receptors known to play a role in autonomic regulation have also been observed to influence renin release, for example carotid sinus baroreceptors (Hodge, Lowe and Vane, 1966; Cunningham, Feigl and Scher, 1978; Powis and Donald, 1979).

However, Brennan, Henninger, Jochim and Malvin (1974) concluded that there is no relationship between carotid sinus pressure and plasma renin, despite earlier findings to the contrary. This negative finding may have been due to inadequate control; Rocchini and Barger (1979) showed that carotid hypotension produces a rise in plasma renin activity, provided renal perfusion pressure is maintained at control levels. Normally, carotid occlusion produces an increase in renal perfusion pressure, and this could compensate for the effect of a low carotid sinus pressure. The theoretical significance of this finding is that it suggests both renal perfusion pressure and carotid sinus pressure influence renin secretion rate, and that the effects are additive. In addition, the two systems presumably have approximately the same degree of influence.

In this simulation there are four basic stimuli subserving renin secretion; autonomic activity (AM), right

atrial pressure (RAP), Sodium flow past the efferent end of the loop of Henle (HNAL), and glomerular capillary pressure (PGC). Partly for simplicity, and partly because of a shortage of relevant information, each is given 25% of total influence under normal circumstances. As is shown below, each stimulus is capable of exerting a significant influence on plasma renin concentrations, and within physiological levels, are capable of counteracting each other. This suggests that under normal circumstances their relative influences are roughly equivalent.

By extrapolation from data for cats (Ammons, Santiesteban, Koyama and Manning, 1980), total renin secretion rate for a 300g rat under normal circumstances is about .00434 ng/s; estimates of half-life vary somewhat, but are generally between 10 and 20 minutes (Hodge, Lowe, Ng and Vane, 1969; Ammons et al, 1980).

Cunningham et al, (1978) showed that a drop in arterial pressure from 110 mmHg to 75 mmHg caused a 37% rise in plasma renin activity. This permits the creation of a tentative relationship between autonomic activity and secretion.

Brennan, Malvin, Jochim and Roberts (1971) showed that increases in right atrial pressure cause significant decreases in plasma renin activity, at least in dogs. On the other hand, Brosnihan and Bravo (1978) showed a relationship between reductions in right atrial pressure, and increases in renin secretion rate. The function used in this simulation, derived from these two papers is shown in block 2.

Renal control of renin release is somewhat less clear. Renin, prior to release into the circulation, is contained in the macula densa cells, which in turn comprise part of the juxtaglomerular apparatus (Guyton, 1976, p.468). Some researchers believe release is mediated by intra-renal baroreceptors; others have suggested the cause is some undetermined feedback from the macula densa cells, probably Sodium concentration in the tubular fluid (Vander, 1967; Davis and Freeman, 1976).

Certainly, mean renal perfusion pressure is a potent stimulus for renin release (e.g. Tobian, Tomboulion and Janecek, 1959). There is evidence that suggests the baroreceptors are in the renal afferent arteriole, probably in the area of the juxtaglomerular cells (Witty, Davis, Johnson and Prewitt, 1971). In the current simulation, pressure in this region is best represented by glomerular capillary pressure (see description of the kidney system). There is some evidence to indicate the nature of the relationship between pressure and renin release rate, for example Schmid (1972) and Gutmann, Tagawa, et al (1973). In addition, Blaine, Davis and Harris (1972) developed a useful, albeit hypothetical, function relating afferent arteriolar stretch to renin release rate. The function derived is shown in block 3. Interestingly, the latter paper also points out that the renal baroreceptor system operates at just below normal pressure. This indicates that the earlier assumption about each major influence contributing to normal activity is reasonable.

Davis and Freeman (1976), among others, have debated in

depth the apparently controversial issue of whether renin release is controlled by renal baroreceptors or some unspecified stimulus to the juxtaglomerular apparatus (the 'macula densa theory'). However, it is probably somewhat simplistic to see renin as being either due to baroreceptors or macula densa Sodium load. There is no reason why both controls should not be present. Ammons et al (1980) and Fray, Johnson and Barger (1977) showed that both carotid sinus pressure and dietary Sodium influence plasma renin activity. The latter influence is most directly explained by assuming a direct relationship between plasma Sodium and renin activity. However, much more direct evidence exists. Thureau, Dahlheim et al (1972) showed that retrograde perfusion of the macula densa with Sodium Chloride solutions influenced renin in the juxtaglomerular cells. Another example is the finding of Shade, Davis, Johnson and Witty (1972) that hypernatremia and hyperkalemia decreased renin release in the normal intact filtering kidney, but not in the non-filtering kidney model; it seems likely that the response in renin was mediated by the macula densa.

Thus there appear to be good grounds for assuming a direct relationship. However, what is the nature of this relationship? It certainly appears to be related to Sodium. Numerous attempts have been made to link renin release and a decrease in the filtered load of Sodium; for a good review of this subject, see Davis and Freeman (1976). However, such attempts have not always been valid. One has to consider additional influences, such as the loop of Henle, through which filtered fluid has to pass before reaching the macula



densa. In addition, there is some uncertainty as to whether the appropriate stimulus is Sodium load or concentration. In this simulation, it was felt that Sodium load may be a better stimulus; the nearest approximation to macula densa load available is rate of Sodium flow from the loop of Henle. Such an approach is similar to that taken by Blaine, Davis and Harris (1972). The function eventually derived is shown in block 4. Block 5 sums the influences on renin secretion due to right atrial pressure, autonomic activity, glomerular capillary pressure and Sodium load at the distal end of the loop of Henle.

However, many other influences on renin release have been observed, and it is worthwhile attempting to incorporate some of them. Unfortunately, the evidence for most is much more fragmentary than the four influences discussed earlier, so this section is somewhat speculative.

Abbrecht and Vander (1970) showed that a decrease in dietary Potassium stimulates renin release, at least in humans. This occurred despite an increase in plasma Sodium concentration. Conversely, an increase in dietary Potassium decreases plasma renin, despite a fall in plasma Sodium (Brunner, Baer et al, 1970). Vander (1970) points out that such releases appear to be independent of any observable changes in renal haemodynamics, apart from Potassium concentration.

Sodium and Potassium often appear to have complementary effects within the same mechanism (e.g. aldosterone). It seemed reasonable therefore to relate the inhibitory effect of Potassium on plasma renin concentration to the flow of

Potassium past the distal end of the loop of Henle, analogous with the stimulus for Sodium-induced renin release. This function is shown in block 6, and its influence is exerted on renin release in block 7.

Both angiotensin and anti-diuretic hormone appear to exert an inhibitory effect on renin secretion rate and plasma renin activity (Tagawa, Vander, Bonjour and Malvin, 1971; Shade, Davis et al, 1972; Blair-West, Coghlan et al, 1971). Both appear to be the result of a direct effect on the juxtaglomerular cells. In the case of angiotensin, the doses are sub-pressor, and thus cannot be attributed to, for example, variations in hepatic blood flow (see later). There does not appear to be any change in intra-renal distribution of blood flow (Carriere and Biron, 1970). These effects are represented in blocks 8 to 11.

A delay between applying a renin-releasing stimulus and the corresponding response has frequently been observed (e.g. Gutmann, Tagawa, Haber and Barger, 1973). These authors reported that maximum renin output is achieved about two minutes after occlusion of the renal artery. Coote, Johns, MacLeod and Singer (1972) indicated a delay of about 11 minutes between renal nerve stimulation and maximal plasma renin activity; the benefit of this report is indirect, however, as this is a consequence not of stimulus-response latency, but of integration. Blocks 12 to 14 represent this stimulus-response delay. The output of block 14 finally gives the renin secretion rate (RSR), in ng/s.

In order to calculate renin concentration however, it is necessary to know the rate at which it is cleared from

the circulation, and its normal volume of distribution. Normal renin half-life is around 15 minutes in rats; it is thought that most is inactivated in the liver. (See Blaine, Davis and Harris (1972) for a discussion of this topic). Thus one would expect the rate of destruction to be related to hepatic blood flow.

Sapirstein, Sapirstein and Bredemeyer (1960) give a relationship between cardiac output (CO) and hepatic blood flow (HBF); the function in block 16 is derived from this. Block 18 calculates hepatic plasma flow (HPF), using hepatic blood flow and haematocrit, derived in block 17. Block 19 applies an estimate of 'proportional clearance', i.e. the proportion of renin entering the liver that is destroyed. This was derived empirically, using current estimates of renin half-life. The output of this block, when applied to block 20, gives the actual destruction rate of renin.

This is not the only means by which renin is lost from the system; an assumption made here is that any renin contained in plasma filtered by the kidney is lost. Although urine is protein-free under normal circumstances, it is assumed that the filtered renin will be inactivated during its reabsorption. Thus block 21 multiplies glomerular filtration rate (GFR, ml/s) by plasma renin concentration to give renin loss by this means. Block 22 sums the two causes of renin loss to give total destruction rate. Net production/destruction rate is derived in block 15.

Block 23 integrates the output of block 15 (REN1, ng/s) to give the total amount of renin in circulation (REN2, ng). It is assumed here that the volume of distribution of renin

is equal to plasma volume (PV). Thus block 24 divides total renin by plasma volume to give plasma concentration (REN, ng/ml).

### Angiotensin I and II Control

As discussed earlier, angiotensin I is split from a plasma protein (renin substrate) by renin. When the angiotensin I, which is a decapeptide, passes through the lungs, it is further split to form the octapeptide angiotensin II under the influence of converting enzyme contained in the lung tissues. This latter form of angiotensin is the most powerful vasoconstrictor substance known (Guyton, 1976).

Blocks 25 and 26 represents the rate at which renin causes the release of angiotensin I from renin substrate. It is assumed that this release rate is directly proportional to renin concentration. The output of block 25 is the conversion rate per ml of plasma. Thus to obtain total conversion rate, block 26 multiplies this by plasma volume (on the assumption that the conversion occurs equally throughout the circulation).

Blocks 27 to 30 simulate the destruction of angiotensin I, which in this case also gives the production rate of angiotensin II. As discussed above, conversion occurs predominantly in the lungs, under the influence of a converting enzyme. Thus, on the assumption that pulmonary blood flow is normally equal to cardiac output, block 28 multiplies cardiac output by blood haematocrit to give pulmonary plasma flow. Block 29 then applies a constant,

derived empirically. In effect, this means that of the angiotensin I that flows through the lungs, 50% is converted to angiotensin II.

Block 31 calculates the net formation rate of angiotensin (ANGI3, ng/s), summing formation and destruction rates. Block 32 integrates net production rate to give total plasma angiotensin I (ANGI4, ng); this, when divided by plasma volume (assumed to be the volume of distribution) gives its concentration, ANGI.

Block 34 derives the net angiotensin II production rate in the usual fashion, and block 35 integrates this to give total angiotensin II. Block 36 calculates the destruction rate of angiotensin II; the constant is derived from Ferreira and Vane (1967- rat) and Guyton (1971- dog). Block 37 derives plasma angiotensin II concentration.

#### Validation of the Renin-Angiotensin System

No additional simulations are presented here to validate the renin-angiotensin system (nor for any other of the hormonal systems). This is because in the real animal (and hence, one hopes, in this simulation) they rarely act on their own. Thus it is felt they are better tested in the whole-animal simulations presented in Chapter 14.

CHAPTER 11Aldosterone SystemIntroduction

This system plays a very important role in extracellular Potassium homeostasis, by regulating its renal secretion. Without a functioning system, the animal can easily die from either hypo- or hyperkalemia (Guyton, 1976, p.481). Considering the nature of negative feedback systems, it is perhaps not surprising that a major determinant of plasma aldosterone concentration is extracellular Potassium concentration. In addition, although some may argue about the magnitude of its influence (e.g. Young and Guyton, 1974), the renin-angiotensin system is also important, and many of the observed influences on aldosterone may exert their effects via this system (Michelakis and Horton, 1970). Considering that the renin-angiotensin system is in turn greatly influenced by autonomic activity, the range of potential factors capable of disturbing aldosterone metabolism is very wide indeed (Laragh, Angers et al, 1960). This may for example be the explanation for the findings of Anderson, McCally and Farrell (1959), who report effects of atrial stretch on aldosterone secretion. Naturally, many effects remain difficult to explain in terms of such a simple model. For example, Share and Claybaugh (1972) noted that during fasting, elevated plasma aldosterone levels occur in the absence of any detectable changes in the factors mentioned above. This, it is felt, could in reality be the consequence

of an alteration in aldosterone clearance, and hence half-life. As with renin, most of the aldosterone present in plasma is cleared by the liver (Schneider, Davis et al, 1970).

Guyton (1976) proposes that the major role of aldosterone is in Potassium regulation alone; Sodium regulation is better catered for by other systems (Young and Guyton, 1974). Some other research, on the rat, tends to support this hypothesis (Boyd, Palmore and Mulrow, 1971).

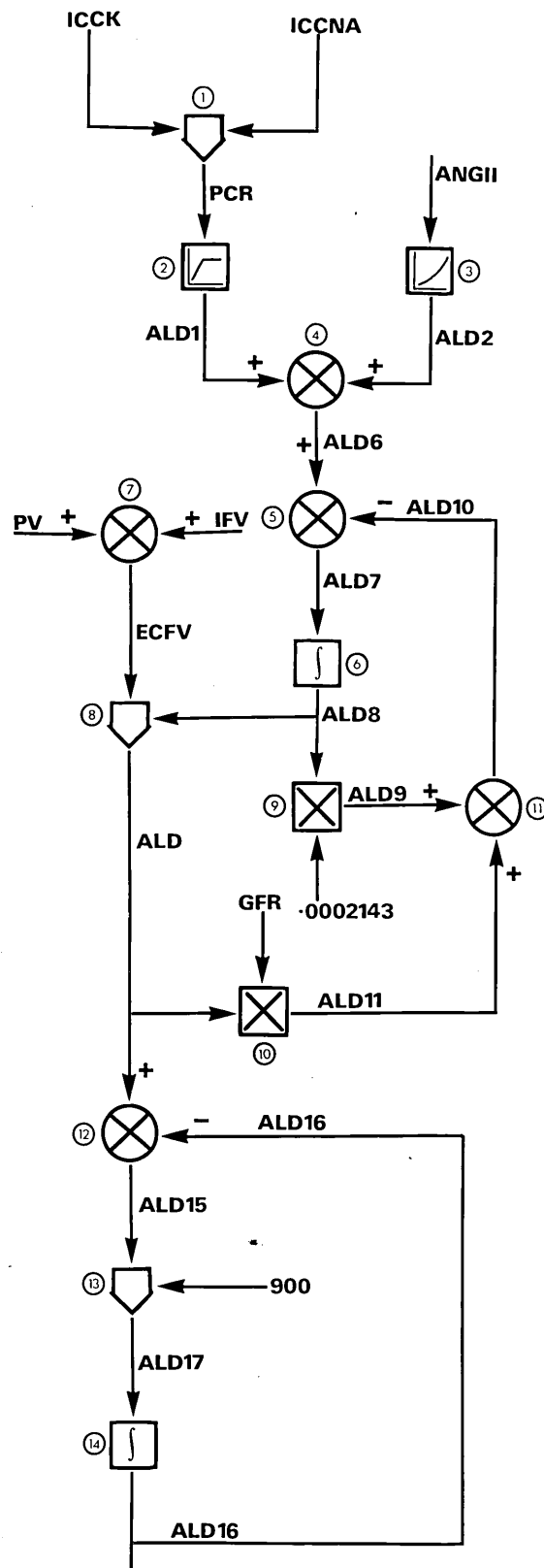
Unfortunately, the mechanism by which Potassium affects aldosterone secretion is not known (Fraser, Brown et al, 1979), so much remains to be resolved.

Fortunately, the situation is a little clearer in the case of angiotensin-induced aldosterone release (e.g. Campbell, Brooks and Pettinger, 1974; Kramer, Gallant and Brownie, 1980).

### System Description

From the above discussion it should be apparent that the system presented here is somewhat hypothetical. Nevertheless, it is hoped that sufficient realism has been achieved for it to be useful.

Guyton, Coleman and Granger (1972), in their massive control system analysis of human fluid dynamics, used not plasma Potassium as such to determine aldosterone secretion, but the Potassium to Sodium ratio. This example has been followed in the simulation presented here, and is represented in blocks 1 and 2 of Fig. 11.1. It may well be wrong; a differing (though slightly less clear) approach has



## Aldosterone System

FIGURE 11.1



been taken by Blaine, Davis and Harris (1972) in their steady-state analysis of the renin-angiotensin-aldosterone system. The function used is derived from Guyton (1976-dogs) p.482, and Corvol, Oblin et al, (1977- rats).

The other stimulatory influence represented here, that of plasma angiotensin II, is shown in block 3. The relationship is derived from data presented by Campbell, Brooks and Pettinger (1974), Cowley and McCaa (1976), and Fraser, Brown et al (1979).

It is tentatively assumed that the two effects are additive, and thus block 4 sums the influences of plasma Potassium/Sodium ratio and angiotensin II, to give total aldosterone secretion rate (ALD6). The 'evidence' for assuming additivity is tenuous to say the least, being based upon similar additivity observed in the anti-diuretic hormone system (Johnson, Zehr and Moore, 1970). For the most part however, one is merely assuming the simplest system whilst tolerating a lack of any contradictory evidence. A similar additive system was employed by Guyton, Coleman and Granger (1972). That the system may in fact be very complex is indicated by the review of Fraser, Brown et al (1979). This apparent complexity may however be due more to the machinations of the renin-angiotensin and autonomic systems than any lack of stimulus additivity in the aldosterone system.

Block 5 sums total production and destruction (clearance) rates of aldosterone, to give the net production rate. Block 6 then integrates this net production rate, yielding total extracellular aldosterone. Aldosterone, by

biochemical standards, is a small molecule (a steroid). Consequently, it is assumed that it is easily capable of crossing the capillary walls and entering the interstitial compartment. In other words, its volume of distribution is total extracellular fluid, rather than just plasma. Block 7 accordingly sums plasma and interstitial fluid volumes, and block 8 derives the concentration of aldosterone in this total volume.

Clearance of aldosterone from the circulation can occur by two means in this simulation; 'natural' decay (emulating hepatic loss) (Schneider, Davis et al, 1970) and glomerular filtration. Hepatic losses are estimated by block 9. It is assumed that all aldosterone contained in glomerular filtrate is in effect lost from the system. This is not to say that it will appear in the urine, although some does (Corvol, Oblin et al, 1977). However, it is anticipated that the process of renal reabsorption of filtered aldosterone will result in its degradation to metabolites. Thus block 10 multiplies glomerular filtration rate by plasma aldosterone concentration, to give renal aldosterone clearance. Block 11 sums hepatic and renal clearances, yielding the total aldosterone destruction rate.

The means by which aldosterone influences renal inorganic ion reabsorption is complex, and gradual. Basically, aldosterone combines in the renal tubular cells with a receptor protein. This then diffuses into the nucleus, where it activates DNA to form the appropriate messenger RNA molecules. This RNA is responsible for manufacturing the proteins necessary for Sodium and

Potassium transport.

The practical significance of all this is that there is a delay of at least 45 minutes between an increase in plasma aldosterone and the corresponding increase in tubular ion transfer. This is represented by blocks 12 to 14, which subjects the effects of plasma aldosterone to an exponential delay.

Thus whilst the output of block 8 represents plasma aldosterone concentration, block 14 provides the more important value, representing the renal response to that aldosterone concentration.

CHAPTER 12Anti-Diuretic Hormone ControlIntroduction

The system presented here is bound to be a simplification. ADH is likely to be a neurotransmitter (Buijs and Swaab, 1979), and thus its effects are probably legion. For example, ADH and related hormones affect memory processes in rats (Van Wimersma Greidanus et al, 1975; de Wied et al, 1976). The reasons for this are unclear, although a possible anatomical basis has been elucidated (Buijs and Swaab, 1979).

Similarly, the mechanisms of synthesis, transport and release are ignored, except to the extent that they may cause a time delay between a stimulus and the secretory response. For more information, see Kleeman and Vorherr (1974), and Brownstein et al (1980).

The assessment of normal plasma ADH concentration has become feasible only within the last 10 years or so, with the development of sufficiently sensitive radioimmunoassays. The bioassays previously available (e.g. Ginsburg and Heller, 1953) could only assess the greatly increased ADH concentrations resulting from physiological intervention. In addition, many early experiments on ADH metabolism included operative procedures and the use of anaesthetics, both of which greatly increase plasma ADH levels, e.g. Ginsburg and Brown, (1956); Little and Radford, (1964); Vorherr et al, (1968); Dogterom et al, (1978). thus, as Verney (1958) points out, representative assessments can only be made when

the animal is 'unbenumbed by the state of anaesthesia'.

Even posture has been shown to have an influence on plasma ADH in humans (Segar and Moore, 1968; Moore, 1971), presumably a venous baroreceptor-mediated effect.

Dyball (1968,1971) reported normal plasma ADH of up to 500 pg/ml. However, the use of more recent radioimmunological techniques have shown that this is much too high; the consensus seems to be that normal (rat) plasma ADH is between 2 and 5pg/ml. (Dogterom et al, 1978; Dunn et al, 1973; Haack et al, 1977, and Mohring et al, 1978). Severe dehydration appears to increase ADH concentration to about 25-30 pg/ml in rats (Dunn et al, 1973).

As Bie (1980) points out, these differences are more likely to be due to experimental, rather than assay techniques. This excellent review gives further details of ADH metabolism, and its control.

The following sections describe the system subserving ADH metabolism developed for this simulation. It is, as far as one can gather, entirely original, and is illustrated in Figure 12.1.

#### The Volume of Distribution of ADH

Lauson and Bocanegra (1961), cited by Fincham (1963), showed that the volume of distribution of Pitressin (a commercial preparation of ADH) in dogs is about 14% larger than the plasma volume. This finding is corroborated by Czaczkes and Kleeman (1964), who also found that ADH distribution volume approximated to the assumed plasma volume.

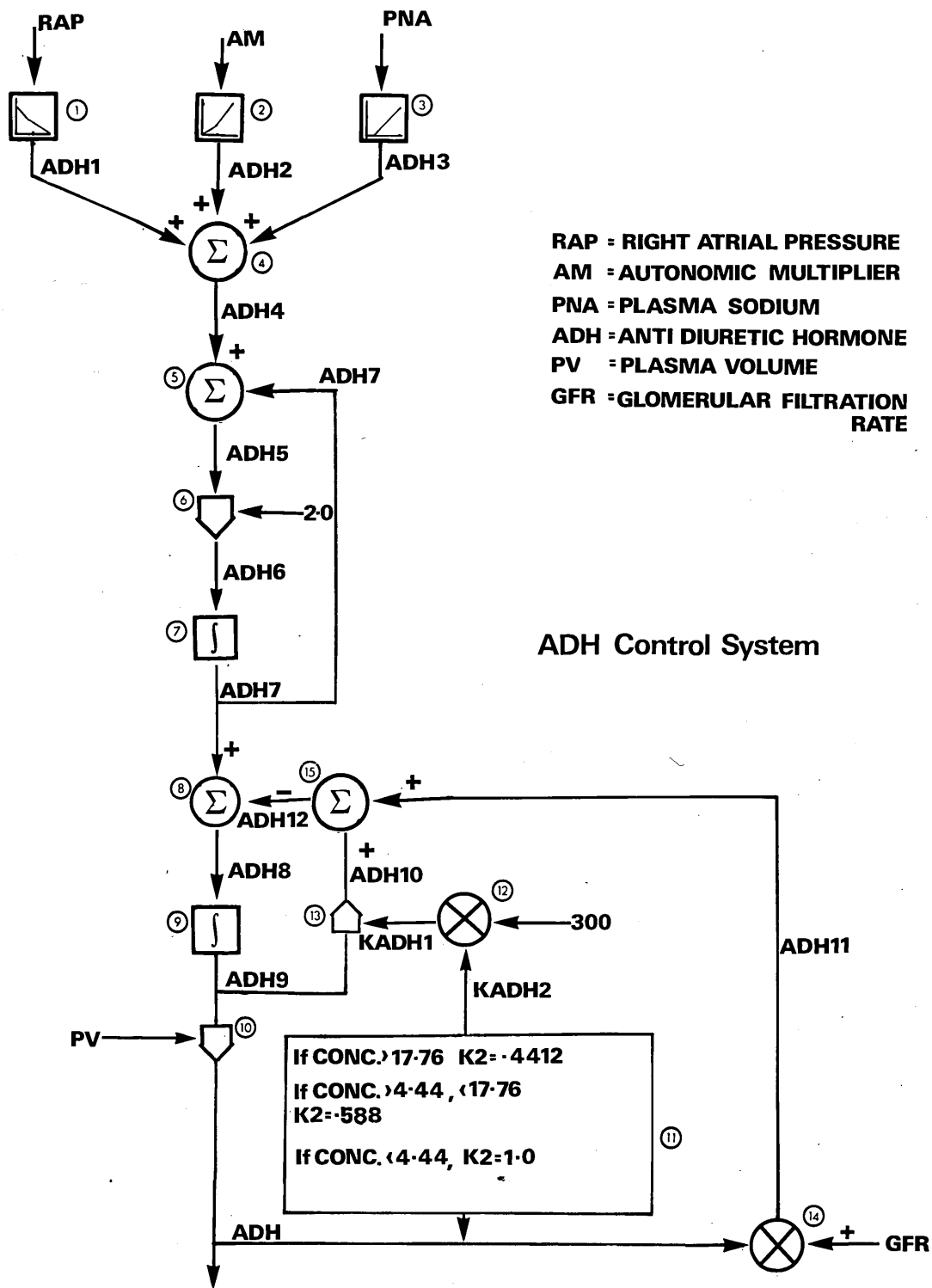


FIGURE 12.1

Errington and Rocha e Silva (1972) conclude however that the apparent distribution space of ADH is considerably larger than plasma volume, but not as great as plasma plus interstitial fluid (i.e. extracellular) volume. The distribution space they have in mind probably corresponds to plasma plus the 'free liquid' portion of interstitial fluid. This fraction could reasonably be expected to vary considerably as a function of hydrational state.

The apparent contradiction between the reports of Czaczkes and Kleeman (1964) and Errington and Rocha e Silva (1972) may be resolved by a study of the experimental techniques employed. Both induced high concentrations of ADH, and then studied the decline in concentration over time. However, Czaczkes and Kleeman (1964) achieved high plasma concentrations by a steady infusion of arginine-vasopressin (Pitressin), whereas Errington and Rocha e Silva (1972) achieved theirs by haemorrhage. Results obtained by use of the latter technique cannot so easily be generalised to other physiological conditions, due to the wide range of cardiovascular responses elicited. The question of why ADH apparent distribution space should be greater following haemorrhage than normal conditions is itself of interest and deserves further investigation.

Czaczkes and Kleeman (1964) substantiate their comments on distribution volume by finding less than 1 micro Unit of ADH per ml of lymph at a time when the plasma level was above 200 micro Units per ml.

The Half-Life of ADH

Here again there is an apparent conflict between the data of Czaczkes and Kleeman (1964) and Errington and Rocha e Silva (1972). The former found in both rat and dog that at higher plasma concentrations of ADH turnover of the hormone was more rapid. Thus half-life shortened as concentration increased. Under normal circumstances, ADH half-life was around 3.4 mins.

On the other hand, Errington and Rocha e Silva (1972) found that ADH half-life was significantly longer when concentration was high (i.e. in early stages of shock following haemorrhage), and normal half-life was around 5 minutes. This is in agreement with Fabian et al (1969), who reported an ADH half-life of 5.6 minutes.

The easiest problem to resolve is probably that of normal half-life. Errington's experiments were conducted on dogs, Czaczkes' on rats. However, the latter author also showed in the above-mentioned paper that there is a definite relationship between body size and ADH fractional turnover rate. Thus one would expect a small animal, such as a rat, to have a shorter ADH half-life than a large animal, such as a dog. A similar conclusion was reached by Lauson and Bocanegra (1961). One could conjecture that the half-life of ADH is related to blood circulation time.

Possibly one can explain these differences by considering the cardiovascular responses to haemorrhage. Lauson (1967) showed that the kidney and liver are the major sites of inactivation of ADH, each organ clearing or inactivating approximately equal amounts of the ADH present



in the blood circulating through it. (In the present model, extra-renal ADH destruction is simply determined as a function of plasma concentration. In future however, the system will be adapted to incorporate the influence of any variations in hepatic blood flow.) Apparently about 10% of the hormone secreted is excreted by the kidney in active form, which raises the interesting question of why ADH should be so ineffective at crossing the capillary walls, but be able to pass through glomerular slit-pores with such ease?

Thus it can be conjectured that in haemorrhage the blood flow through these organs would be reduced by vascular constriction, thus reducing destruction, and lengthening ADH half-life. Such phenomena have been observed in the rat liver and kidney by Sapirstein et al (1960). This would not occur to such an extent in the case of dehydration, due to the gradual nature of stimulus onset, or during the infusion ADH, as conducted by Czaczkes and Kleeman (1964).

Thus for the purposes of the system developed here, the data of Czaczkes and Kleeman (1964) was adopted.

#### Osmotic Influences on ADH Release

The classic work of Verney (1947) showed that intracarotid injections of hypertonic saline elicited a reduction in diuresis, caused by a release of anti-diuretic hormone. Quantitative relationships, however, are a little more difficult to come by. Dunn et al (1973) (rats) and Schrier et al (1979) (humans) both show linear relationships between plasma osmolality and plasma ADH concentrations. The

regression line for Dunn's (1973) rat data is somewhat steeper than for the human data of Schrier-as one would expect it to be for an animal that conserves water more efficiently than man.

This does not mean however that the function relating plasma osmolality to ADH secretion is linear, especially as ADH half-life is not constant (see earlier section).

In an early computer simulation of renal dynamics, Fincham (1963) assumed that changes in plasma Sodium concentration per se influenced ADH secretion. Toates and Oatley (1970) also employed plasma Sodium concentration, but considered this effect to be mediated by an osmoreceptor cell, the essential role of which is to signal the state of the intracellular fluid compartment. However, without wishing to become involved in the semantics of such an argument, the present author considers it unlikely that the supra-optic nuclei can act as an average member of the intracellular compartment. Supra-optic neurones are in intimate contact with capillaries in possibly the most densely vascularized region of the brain, (Sofroniew and Glassman, 1981), and thus one would expect them to be affected by a change in plasma osmolality much more quickly than the vast majority of the body's cells, which are buffered from these influences by the interstitial fluid. This in no way detracts from their importance; however, they should be more properly regarded as an early warning system giving notice of changes in plasma osmolality, rather than a representative of average cell state.

Baroreceptor Influences on ADH Release

A major physiological stimulus for ADH release is a change in blood volume. This acts primarily via stretch or baroreceptors in the left atrium of the heart. (Share and Claybaugh, 1972). For the purposes of this simulation, it is assumed that influences on ADH secretion from baroreceptors in other sites (e.g. carotid sinus) are mediated by autonomic activity. This system is discussed in the next section.

A second assumption made is that right atrial pressure will approximate to left atrial pressure. The reason for this is that the current simulation does not incorporate a pulmonary circulation, and thus is not capable of calculating left atrial pressure. The available evidence suggests however that this assumption is a valid one, at least within the ranges experienced under normal physiological conditions. Over reasonable ranges, right atrial pressure is an acceptable substitute for left atrial pressure.

The actual receptors involved appear to be Type B left atrial receptors (Paintal, 1953). These may also influence heart rate, at least in dogs (Ledsome and Linden, 1967).

Johnson, Moore and Segar (1969) showed that increases in left atrial transmural pressure produced a decrease in plasma ADH concentration. This experiment corroborated and extended the report by Lydtin and Hamilton (1964), which found that tightening a purse string around the mitral valve would increase the flow of urine.

However, does a decrease in left atrial pressure elicit

the corresponding increase in ADH secretion? To study this question, Goetz, Bond et al (1970) used the atrial tamponade, a technique whereby the atrium is surrounded by a pouch. (For a complete description of this technique, see Goetz, Hermreck et al, 1970). The transmural pressure can then be varied by infusing isotonic saline into the pouch, to match atrial pressure.

With this technique, decreases in atrial transmural pressure did not increase ADH concentration, although urine flow and Sodium excretion did decrease. However, the receptors involved may have been on or near to the edge of the pericardial pouch, and would thus be little affected by the mean decrease in transmural pressure. This possibility is tentatively supported by the findings of Henry, Gupta, Meehan and Sinclair (1968). Following a small haemorrhage, venous pressure drops, whereas arterial pressure remains unchanged; the latter is better defended by the circulatory system (Gupta et al, 1966; Henry, Gupta et al, 1968). Henry et al (1968) showed that such a non-hypotensive haemorrhage, which could therefore only stimulate venous receptors, causes an increase in plasma ADH concentration. This finding is supported by Gupta, Henry, Sinclair and Von Baumgarten (1966) who, in a study of atrial and aortic Type B baroreceptors showed that aortic receptor firing rate does not alter greatly following a 10% (moderate) haemorrhage, but atrial receptor firing rate does. In addition, plasma ADH concentration increases.

There is, however a possible objection to this argument. Earlier, it was argued that the data of Errington

and Rocha e Silva (1972) were not acceptable for the purposes of this simulation because the technique used to induce high levels of plasma ADH, i.e. haemorrhage, elicited a wide range of cardiovascular responses. One of these was probably vasoconstriction of the renal and hepatic arteries. The consequent reduction in ADH destruction rates could account for the observed increase in ADH half-life. Is it not therefore possible that the increased ADH concentrations observed following non-hypotensive haemorrhage occur because of atrial receptor-induced renal and hepatic arterial vasoconstriction?

However, there are some difficulties with this line of attack. First, the haemorrhages used to study organ blood flow (Sapirstein et al, 1960) are much greater than those used by the above-mentioned researchers studying atrial receptor responses. Secondly, there is no evidence to suggest that atrial Type B receptors are involved in vasoconstrictive responses to haemorrhage, although of course none of the above studies excite Type B receptors specifically. Thirdly, the extent of renal and hepatic vasoconstriction would have to be great in order to produce the observed increases in ADH concentration. Fourthly, and somewhat teleologically, if one is to have an ADH system that can respond to a reduction in blood volume, it makes sense to site the receptors in a position where they can readily detect any changes, i.e. in the venous circulation.

Thus, for the purposes of this simulation it was decided to have an atrial pressure/ADH release function. It should be borne in mind however, that future work, or studies as

yet unearthed may render this subsystem unnecessary.

With reference to the work of Gupta, Henry, Sinclair and von Baumgarten (1968), an additional assumption made is that ADH release rate is directly related to atrial receptor firing rate. Thus the 'gain' of this system is far greater for reductions in atrial pressure than for increases.

The relationship between right atrial pressure and ADH secretion rate used in this simulation is derived from the data provided by Henry et al (1968) and Johnson, Moore and Segar (1969). It represents the best possible fit to the two sets of data, each of which cover a different range of atrial pressures.

From the data on aortic and atrial receptor firing rates following graded haemorrhages (Gupta et al, 1966), one is lead to the conclusion that whilst arterial receptors can exert a considerable influence on ADH release, they only do so under extreme circumstances. Under normal conditions, the atrial receptors predominate. A similar conclusion has been reached by Rocha e Silva et al (1978), in a mathematical modelling of vasopressin secretion in response to haemorrhage, and by Share (1967); Share and Claybaugh (1972). The latter experiment was far from conclusive however, as the subjects (dogs) were subjected to anaesthesia and surgery, both of which induce artificially high plasma ADH concentrations. As mentioned earlier, the influences of arterial baroreceptors on ADH release are mediated via the autonomic system in this simulation.

Autonomic Influences on ADH Release

Physiological stress of any kind (e.g. surgery) tends to dramatically increase plasma levels of ADH. See earlier discussions, and Errington and Rocha e Silva (1972). Presumably this response is elicited by the autonomic nervous system (here referred to as the autonomic multiplier, AM, in deference to Guyton and Coleman (1967)).

In addition, it has been demonstrated that various arterial baroreceptors (e.g. carotid sinus receptors; Share, 1967) can influence ADH secretion rate, if blood loss is great enough for the arterial receptors to respond.

Thus as arterial baroreceptor responses are a major component of AM activity, it was considered most parsimonious to use AM as the representative of arterial baroreceptor influence on ADH secretion. This, it later transpired, was also the approach adopted by Guyton, Coleman and Granger, (1972) in their analysis of cardiovascular regulation.

The AM/ADH secretion rate function developed here is somewhat hypothetical; no information is available. However, it has been assumed that;

- a) Normal AM (1.0) contributes a little to ADH release.
- b) A 20% blood loss causes an increase in AM of about 0.3, and that this produces an ADH concentration of about 40 pg/ml.

The former and latter assumptions have been verified by Dunn et al (1973).

CHAPTER 13The Autonomic Nervous SystemIntroduction

Several simulations, most notably those of Arthur Guyton and his colleagues (e.g. Guyton and Coleman, 1967; Guyton, Coleman and Granger, 1972) have incorporated representations of the autonomic nervous system. Although the latter simulation embodies a much more complex system than the former, both treat autonomic activity as a unitary phenomenon, and do not consider such topics as reciprocal innervation by the parasympathetic nervous system. This is most probably a consequence of the particular aspect of autonomic activity in which one is most interested, i.e. cardiovascular effects (see the corresponding introductory discussion for the 'small rat'). Although the simulation described here is somewhat more complex than most autonomic representations, it was decided on grounds of parsimony to use the same technique as Guyton in his publications. Thus the final output of the autonomic system described here is termed the 'autonomic multiplier'. The normal value is one; values greater than this indicate excitation, and lesser values indicate inhibition. The autonomic nervous system in effect forms part of a negative feedback loop serving (in this case) to maintain normal arterial pressure. Such an extensive system of negative feedback loops demand an equally extensive set of sensors indicating body state. Accordingly, the model presented here possesses arterial and venous baro-receptors, plus chemoreceptors. Collectively,



these accurately reflect the state of the cardiovascular system.

Each type of receptor has different response characteristics, especially in terms of their responses to long-term stimulation. The interactions of these, studied in conjunction with the hormonal control systems of the body, may provide clues to the nature of such perplexing problems as hypertension. Such a complex system is best analysed using a computer; by hand, the best one can hope for is analysis of steady-state responses, in which equilibrium has already been reached. In many clinical states however, it is the dynamic responses to a state of disequilibrium that are frequently of greater interest.

#### Baroreceptor Influences on Autonomic Activity

In this system, three types of baroreceptor are represented; carotid, aortic and atrial stretch receptors. This is similar to the approach taken by Guyton, Coleman and Granger (1972), except that in this case venous receptors are included. The baroreceptors will be described in the order given above.

The secretion rate of anti-diuretic hormone is partially determined by the behaviour of arterial baroreceptors. Berl, Harbottle et al (1974) showed that intra-venous infusions of norepinephrine caused an ADH-related diuresis, whereas intra-carotid infusions did not (the brain would have destroyed the norepinephrine). This suggested the presence of an extra-cerebral reflex, and thus suspicion fell on the baroreceptors. Further, Berl,

Harbottle et al (1974) showed that selective denervation of the carotid sinus baroreceptors prevented the diuresis normally found after intravenous norepinephrine infusion.

As discussed elsewhere, another determinant of ADH release is atrial pressure. The relaxation of the atrial stretch receptors elicits an increase in ADH secretion (Vander, Sherman and Luciano 1975, p.337; Guyton 1976, p.1001).

As far as the cardiovascular system is concerned, the aims of the autonomic nervous system and the anti-diuretic hormone system are complementary. During periods of dehydration, the former will reduce the compliance of the vasculature, and the latter will reduce renal loss of fluid. Thus it seems reasonable to suspect that the same receptors (or at least receptors in similar sites and with similar response characteristics) subserve both autonomic activity and ADH release. Consequently some of the research conducted on response characteristics of baroreceptors subserving ADH release has been used to assist in the development of the autonomic system. Additional evidence in favour of this assumption is provided by Thames and Schmid (1981), who showed that alterations in carotid sinus pressure influence arterial pressure and plasma ADH concentration concurrently. Direct evidence of the role played by carotid sinus baroreceptors is given by Guyton, Batson et al (1951), Ross, Frahm and Braunwald (1961), and Chalmers, Korner and White (1967). Incidentally, Thames and Schmid (1981) also show that the carotid sinus receptors interact with cardiopulmonary receptors in both ADH and arterial pressure

regulation.

The carotid sinus baroreceptors appear to have a multitude of effects. Thus they have been observed to influence plasma levels of renin (Thames, Jarecki and Donald, 1978; Thames, 1978; Cunningham, Feigl and Scher, 1978; Jarecki, Thoren and Donald, 1978). More recent research has indicated that this is probably mediated by the autonomic nervous system (Schultz, Zehr and Livnat, 1982). This may also be the case with the observed effects of carotid sinus nerve stimulation on cardiorespiratory responses (Levy and Zieske, 1976).

It is assumed in addition that the magnitude of any particular baroreceptor's effect on autonomic activity is inversely related to that baroreceptor's firing rate.

The relationship between arterial pressure and carotid sinus baroreceptor response is derived from Landgren, 1952, Spickler and Kezdi (1967), Koushanpour and McGee (1969), and Donald and Edis (1971). The functions provided in these papers are very similar to each other, although Landgren (1952) does highlight the importance of pulse pressure (rather than a constant pressure). (For additional information, see also Ead, Green and Neil, 1952). This is perhaps not surprising, considering their normal working environment. This aspect of their behaviour has since been studied in greater depth by Angell James (1968, 1971a, 1971b; Angell James and De Burgh Daly, 1970). Although the model presented here cannot hope to simulate such transient phenomena as pulse pressures, the function used is a good approximation to the carotid baroreceptor characteristics

reported by the above authors.

It should perhaps be pointed out that the functions given in this section are frequently the inverse of the pressure/neural firing rate functions presented by cited authors. This is because an increase in pressure will elicit an increase in firing rate; this serves to decrease the aspect of autonomic activity in which one is interested.

Following stimulation, receptors always take a certain amount of time before responding maximally; they show a stimulus-response latency. The stimulus-response latency of carotid sinus baroreceptors is represented by blocks 2 to 4 of Fig. 13.1. In effect, this imposes an exponential delay on the baroreceptor's response to a change in arterial pressure. Some evidence regarding the normal magnitude of this delay is given by Guyton (1948; 1976, p.279). Unfortunately this data is derived from dogs and humans, but it is currently the best available. Additional information on a related topic is given by Levy and Zieske, (1976). Note that the stimulus-response time as used here refers to the time taken for the results of receptor stimulation to be felt, be it in terms of ADH release or vasoconstriction. It does not refer to the very much shorter intervals between stimulation and an increase in receptor firing rate.

The appropriately delayed signal, representing the contribution of carotid sinus baroreceptors to total autonomic activity, is output by block 4.

The carotid sinus receptors communicate with the brain via Hering's and thence the glossopharyngeal nerve. For an excellent review of these and other 'reflexogenic' areas of



the cardiovascular system, see Heymans and Neil (1958). There are other arterial sites richly endowed with baroreceptors; one is the aortic arch. The receptors here communicate with the brain via the vagus nerves. (Guyton 1976, p.268). These too contribute towards autonomic activity, and their pressure/response relationship is given in block 5. Both carotid sinus and aortic baroreceptors are stretch receptors, responding to increases of arterial pressure with increased firing. Their individual firing rate increases almost linearly with mean pressures from 40 to 150 mmHg (Heymans and Neil, 1958). However when studying the combined response the increase follows an S-shaped curve, on account of the different thresholds of individual receptors (Aars, 1968).

Donald and Edis (1971) compared the responses of aortic and carotid baroreceptors in the dog, and concluded that the two are not equivalent. The carotid sinus pressure-response ('Blutdruck-Charakteristic') was symmetrical about the range of normal blood pressure, whereas the aortic arch curve was displaced to the right. This suggests that under normal circumstances the carotid baroreceptors predominate. The aortic baroreceptors contribute under more extreme conditions of relatively severe hypertension.

Interestingly, the aortic baroreceptors are also capable of stimulating ADH release (Schrier, Berl and Anderson, 1979), further suggesting an autonomic role in its regulation.

In this simulation, both types of baroreceptor (and the carotid body chemoreceptors, discussed below) are stimulated

by arterial pressure, despite their being positioned at some distance from the heart. This, it is felt, is a reasonable assumption. The steepest part of the systemic pressure gradient occurs in the capillary beds, and the pressure drop from the heart to the receptors is considered to be negligible.

Thus the relationship shown in block 5 uses arterial pressure as input. The function is derived from Donald and Edis (1971). The relationship given by Donald and Edis (1971) suggests that the aortic baroreceptors contribute little towards arterial pressure regulation during periods of hypotension; they are largely silent when arterial pressure is normal, so they cannot do much at pressures less than this. This may not in fact be the case; Angell James (1971- rabbit) showed that single fibre preparations were active at pressures well below normal. However, this may simply have been an unusual fibre, as they do all appear to have differing thresholds. Whatever the role of aortic baroreceptors in regulating normal arterial pressure, it cannot be very great. Fink, Bryan et al (1981) showed that the standard deviation of arterial pressure variations over a period of 24 hours was about 8 mmHg in normal rats, and 14.4 mmHg in aortic baroreceptor-denervated rats. When constructing such systems as these, it is important to try to ascertain the relative contributions to total autonomic activity made by individual components. The findings of Donald and Edis (1971) suggest that, at least in terms of their relative firing rates, the aortic baroreceptors are not as important as the carotid sinus receptors. This

perhaps rather dangerous assumption is lent a little more credence by Donald and Edis' (1971) findings that the effects of both receptors are additive. Thus it is considered appropriate to give the aortic receptors half the total influence available to the carotid receptors.

As with the carotid receptors, it is necessary to derive a delay circuit, emulating the stimulus-response latency of the aortic receptors. Douglas, Ritchie and Schaumann (1956) electrically stimulated the rabbit aortic nerve, and found that the time taken for the cardiovascular response to reach its greatest strength was about thirty seconds. Similarly, the data of Angell James and DeBurgh Daly (1970) indicate a stimulus-response latency of about thirty seconds in dog carotid and aortic receptors. This delay system is represented by blocks 6 to 8.

One type of baroreceptor not used by Guyton, Coleman and Granger (1972) in their simulation of human cardiovascular dynamics is a venous receptor. There are however, reasonable grounds for including them in any general simulation of this nature. The venous part of the systemic circulation is greatly influenced by autonomic activity, and it would not appear to be in the nature of feedback systems for some venous receptors not to be incorporated. In addition, there is a considerable body of evidence to suggest that the venous side is more sensitive to variations in blood volume (this subject is dealt with briefly by Paintal, 1973). This would make the venous side of the circulation a good candidate for receptors subserving normal arterial pressure regulation. Gupta, Henry et al



(1966) have shown that atrial type B receptors respond (by reducing their firing rate) to much smaller graded haemorrhages than can be detected by aortic receptors. The authors also studied the effects of increasing blood volume on atrial and aortic firing rates, and found again that the atrial receptors were much more sensitive.

As with arterial receptors, their atrial counterparts influence many hormonal and vascular control systems, heavily implicating the autonomic nervous system as a mediator.

Brennan, Malvin et al (1971) showed that increases in right atrial pressure produce a significant decrease in plasma renin; on the other hand, left atrial receptor stimulation is necessary to bring about a drop in plasma ADH concentration. Brosnihan and Bravo (1978) provided support for these findings. They showed that decreases in atrial pressure produces an increase in plasma renin concentration, thus demonstrating their role in both hypo- and hypertension.

Finally, Munzner, Ward and Gann (1981) have shown that signals from right atrial receptors mediate reflex vascular responses. Normally however, these signals are normally masked by those from carotid receptors. Furthermore, these atrial signals are carried by the vagus nerve. Vagotomy has been observed to remove atrial receptor influences on both vasomotor responses and plasma renin (Munzner et al, 1981 and Annat et al, 1976 respectively).

The function relating right atrial pressure to venous baroreceptor activity is derived from Gupta, Henry et al

(1966) and Henry, Gupta, Meehan and Sinclair (1968). It is incorporated in block 9.

As with the other baroreceptors, it is necessary to represent the delay between receptor stimulus and the vasomotor response. Some idea of the stimulus-response latency is provided by Munzner et al (1981), who have shown that receptor stimulation produces a maximal vasomotor response in about 40 seconds. This value has been used in the development of the delay system, represented by blocks 10 to 12.

Block 13 sums the effects of the three baroreceptors so far described. Their influences are assumed to be additive, a reasonable assumption confirmed by the majority of papers cited above. No evidence has yet come to light indicating that the nature of their interaction, at least at this neuronal level, is anything but additive.

#### Chemoreceptor Influences on Autonomic Activity

Baroreceptor responses are not the only ones involved in autonomic and cardiovascular regulation. The two further systems represented here are carotid body chemoreceptors and the central nervous system (C.N.S.) ischaemic response.

Blocks 14 to 19 represent the chemoreceptor responses to a reduction in arterial pressure.

The primary role of the chemoreceptors is in respiratory control. Situated in the carotid and aortic bodies, they respond to changes in arterial oxygen, carbon dioxide and hydrogen ion concentration.

The carotid bodies are located in the bifurcations of

the common carotid arteries. As with the carotid baroreceptors, their afferent fibres pass through Hering's nerve and thence to the medulla via the glossopharyngeal nerve. The chemoreceptors respond strongly to a drop in arterial oxygen pressure (Hornbein, Griffio and Roos, 1961; Biscoe, Purves and Sampson, 1970). The effect of this stimulation is to increase respiratory activity.

However, their role is not confined to respiratory regulation. Landgren and Neil (1952) showed that as arterial pressure falls, blood flow through the carotid body decreases. The resultant stagnant anoxia causes an increase in chemoreceptor discharge. Thus they contribute to the autonomic response to (say) hypovolemia. Chemoreceptor discharge causes vasoconstriction. It does not however cause an increase in cardiac sympathetic impulses; this effect (resulting in an increase in heart rate) appears to be mediated by baroreceptors alone (Downing and Siegel, 1963).<sup>\*</sup> Wherever tachycardia is observed following chemoreceptor stimulation, it appears to be a secondary response, caused by the stimulation of respiration (Comroe, 1939).

The role of chemoreceptors in arterial pressure regulation under normal circumstances is unclear, but they do affect bodily responses under emergency conditions. This is illustrated by a further fall in arterial pressure following haemorrhage after interruption of the chemoreceptor afferents (Comroe, 1939; Kenny and Neil,

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<sup>\*</sup> For this reason, the autonomic activity applied to the heart is a corrected version, removing chemoreceptor influence.

1951). Some evidence is available indicating their role under more normal circumstances. Denervation of the chemoreceptors makes the cardiovascular system distinctly unstable in response to even small haemorrhages. (Remington, Hamilton et al, 1950; Oberg, 1964 and Haddy, Scott and Molnar, 1965).

Some contradictory findings have been published. Thus Acker, Keller and Lubbers (1973) reported that large variations in carotid body flow had no influence on local oxygen pressure or chemoreceptor activity. Arterial pressures below 60mmHg were however accompanied by increased chemoreceptor activity, although with a much reduced sensitivity (Biscoe, Bradley and Purves, 1970). This apparent anomaly may have been resolved by Howe and Neil (1973), who suggested that chemoreceptor activity will increase during hypotension because of sympathetic vasoconstriction of the carotid body vessels. This argument is lent greater weight by Floyd and Neil (1952) who showed that the increase in vasoconstriction subsequent to a haemorrhage adds to the reduction in chemoreceptor blood flow.

This and other subjects related to chemoreceptors are ably reviewed by Chien (1967) and Oberg (1976).

It is apparent from the above discussion that the major determinant of chemoreceptor activity is blood gas balance, mediated by carotid body flow rate, rather than arterial pressure per se. Thus blocks 14 and 15 represent an attempt to relate arterial pressure and carotid body blood flow. The flow is derived by applying a (hypothetical) value of

carotid body resistance. Originally this was partially determined by the level of autonomic activity; a valid assumption, considering the findings of Floyd and Neil (1952). However, this was found to produce some rather odd chemoreceptor response functions, so the influence was removed 'pending further investigation'.

The relationship between carotid body blood flow (output by block 15) and chemoreceptor response, shown in block 16, is derived from Hornbein, Griffio and Roos (1961) and Biscoe, Purves and Sampson (1970). It is interesting to note that the baroreceptors responded to a decrease in arterial pressure by a drop in firing rate; therefore their representations given here are inverted versions of the original. The chemoreceptors respond to a decrease in arterial pressure (ultimately) with an increase in firing rate. Thus the function used here is a direct conversion of the experimental findings.

Assessing the magnitude of the chemoreceptor's contribution to total autonomic activity is not easy, but some idea can be obtained from the further drop in arterial pressure that occurs when the chemoreceptors are inactivated in an already hypovolemic animal. This experiment has fortunately been conducted by Haddy, Scott and Molnar (1965). Their findings are incorporated in the function shown.

As with other receptors discussed in this section, the chemoreceptor systems exhibit a delay between receptor stimulation and their effects being apparent in the cardiovascular system. Somewhat unusually however, there is

some information available to indicate the normal duration of this stimulus-response latency. Hornbein, Griffio and Roos (1961) indicated that maximal cardiovascular response is achieved in about 10 seconds. This has been used in the chemoreceptor stimulus-response system embodied in blocks 17 to 19.

The responses of neither baroreceptors nor chemoreceptors to a stimulus are permanent; they all adapt over time, although at differing rates. The chemoreceptor adaptation system is incorporated in blocks 20 to 27, the corresponding system for baroreceptors in blocks 28 to 34. Both incorporate a 'recovery' routine, enabling a gradual return to normal responsiveness when arterial pressure has returned to normal.

During continuous stimulation, the response of the baroreceptors will decline over a period of days to zero (Guyton, 1976, p.279). When stimulation ceases, they slowly recover their ability to respond. This tendency of the baroreceptors to 'reset' themselves has been implicated in hypertension (McCubbin, Green and Page, 1956).

The chemoreceptors also reduce their output during sustained stimulation, but never cease responding completely. This too is incorporated in the system described in blocks 20 to 27.

The C.N.S. Ischaemic Response

One final influence on autonomic activity, present only in times of severe stress, is the 'C.N.S. ischaemic response'. This has a significant role to play in many experimentally-induced states, such as haemorrhage.

When the blood supply to the brain is very restricted, with arterial pressure below about 60mmHg (Guyton, 1976-dog), the brain becomes ischaemic. This causes the vasomotor centres in the brain to become very active, causing maximal autonomic activity. This is believed to be a consequence of by a build-up of carbon dioxide in the blood, although lactic acid may well also play a part. It is one of the most powerful activators of the sympathetic vaso-constrictor system known. Increases in cerebro-spinal fluid pressure can also bring about a C.N.S. ischaemic response. This is termed the Cushing reaction.

The neurones responsible for creating the C.N.S. ischaemic response appear to reside in the ventrolateral reticular formation of the medulla, at least in the rabbit (Dampney and Moon, 1980). Baroreceptor denervation does not significantly affect the magnitude of most aspects of the ischaemic response.

Some idea of the strength of the response is given by Sagawa, Ross and Guyton (1961). Studying the response of arterial pressure to stepwise decreases in cerebral blood flows, they found increases of up to 180 mmHg above normal in the dog. Dampney and Moon (1980) found responses in the rabbit to be less strong than this, but they used a slightly different experimental technique (direct neuronal

stimulation). Consequently, the two results may not be strictly comparable, although it could as easily indicate the presence of species differences. Some evidence in favour of the latter hypothesis is given by Dampney, Kumada and Reis (1979). Even using similar techniques to those of Sagawa et. al. (1961), they found rabbit responses to be weaker than dog responses. On the principle that the rat is more likely to have similar responses to the rabbit than the dog, the magnitude of the C.N.S. ischaemic response in this simulation is based on the findings of Dampney, rather than Sagawa. Evidence in favour of this conclusion is provided by Sapirstein, Sapirstein and Bredemeyer (1961), who showed that the rat is less tolerant of haemorrhage than the dog. This would be the case if its protective cardiovascular responses were weaker.

In this simulation, the strength of the ischaemic response is related not to arterial pressure or cardiac output per se, but cerebral blood flow. Information enabling one to do this is provided by Sapirstein et al (1961). The function derived is illustrated in block 35. Cerebral blood flow, as one may imagine, is very well protected by the body's cardiovascular responses; indeed it can be argued that this is the primary function of the whole protective system. Thus blood flow remains constant over a wide range of cardiac outputs, and does not reduce until cardiac output is very low indeed.

Block 36 relates the strength of the C.N.S. ischaemic response to cerebral blood flow. The function used is derived from Dampney, Kumada and Reis (1979) and Dampney and



Moon (1980).

As with all other arterial pressure regulatory systems, there is a delay between receptor stimulus and the corresponding response. The response time in the case of the C.N.S. ischaemic response appears to be about 30 seconds (Guyton, 1976, p.279). This stimulus-response latency is represented by blocks 37 to 39.

Again, in a similar manner to the other receptors discussed earlier, the strength of the ischaemic response reduces over a period of time; it adapts. However, the extent of this adaptation is not as great as with the other receptors (Guyton, 1976, p.279). This system, reducing the ischaemic response strength to half its maximal value over a period of about 10 days, is represented in blocks 40 to 46. This also incorporates the system's ability to recover; this is largely a hypothetical system, as no information is available.

Block 47 sums the individual contributions to total autonomic activity from all receptors. Under normal circumstances the sum of these activities is the figure used throughout the simulation to represent autonomic activity. However, there is one remaining circumstance that can drastically alter the effectiveness of the autonomic nervous system.

As mentioned above, the ultimate aim of all these regulatory responses is to maintain an adequate supply of blood to the most sensitive and important part of the body, the brain. For the most part the regulatory systems are successful. However, if they do not succeed, cerebral

ischaemia occurs. This creates the C.N.S. ischaemic response, which can be regarded as a 'last ditch' attempt to restore adequate brain perfusion. If even this does not work, and cerebral ischaemia is very severe, the neuronal cells begin to suffer metabolically. This impairs their ability to respond, and if continued for between three to ten minutes, they will become totally inactive. The autonomic responses will tail off, and arterial pressure drop to a very low value. The animal will die.

The system representing gradual failure of the autonomic system in the face of inadequate brain perfusion is embodied in blocks 48 to 54. The output of the system acts as a 'multiplier', input to block 55. The normal value of this multiplier is one, but brain damage can reduce it to zero.

The main driving stimulus for the system is cerebral blood flow. When this has fallen to a very low value, progressive damage begins to occur, the rate of which is calculated by block 48. This signal gradually reduces the contents of an integrator, represented by block 54. The output of block 54 is the multiplier applied to autonomic activity, and can be regarded as indicating the system's state.

Should the animal be fortunate enough to survive this experience, the damage may not remain permanent. Blocks 49 to 51 permit a gradual recovery, also related to cerebral blood flow; naturally there is a 'cut-off' (block 49) to prevent the recovery signal from occurring whenever no damage has been done. In this way the multiplier output by

block 55 is restricted to an upper limit of one.

However, the capacity for recovery is limited. A small amount of damage is easily reversible, whereas extensive damage is more likely to be permanent, and be proportionately more difficult to repair. This tendency is represented by block 52. The function used is entirely speculative, as no relevant data has come to light.

It is interesting to note that this system initially posed considerable problems in its development. It was only when one considered the system as emulating the demand and supply of a limited (unspecified) neuronal resource that everything 'fell into place'.

#### Validation of the Autonomic Nervous System

Unfortunately, despite its central role, there is a dearth of information on the rat autonomic nervous system. Consequently, no direct comparisons between predicted and experimental data are possible.

However, one may have some faith in it as at least a passable representation. Thus for example, the size of haemorrhage found to be lethal appears to be about right (about 6 ml, withdrawn within a minute); in addition, the system responds as expected to a carotid clamp (see Chapter 4).

CHAPTER 14'Large Rat' SimulationsDrinking in Normal and Food-Deprived Rats

Verplanck and Hayes (1953) studied the drinking behaviour of rats under a variety of feeding and deprivation schedules. They found that rats provided with food 'ad libitum' normally drunk about 31 ml water per day. The same animals deprived of food reduced their daily intake to about 12.9 ml. Partly in order to check the validity of the current model, this experiment was simulated. The results are shown in Table 14.1.

	Expt.	Simulation
Normal	31.3	31.95
Food Deprived	12.94	16.77
Ratio	0.41	0.52

Table 14.1 Daily intake (ml) of normal and food-deprived rats, in day 1

Given that the standard deviation of the experimental findings are about 5 ml in each case, it can be seen that the predicted and actual data are in good agreement. The reasons for a reduced water intake in the food-deprived animal are investigated in the following sections. The data published by Verplanck and Hayes (1953) have been corroborated by that of Bolles (1961).

The drinking pattern shown by the simulation showed a

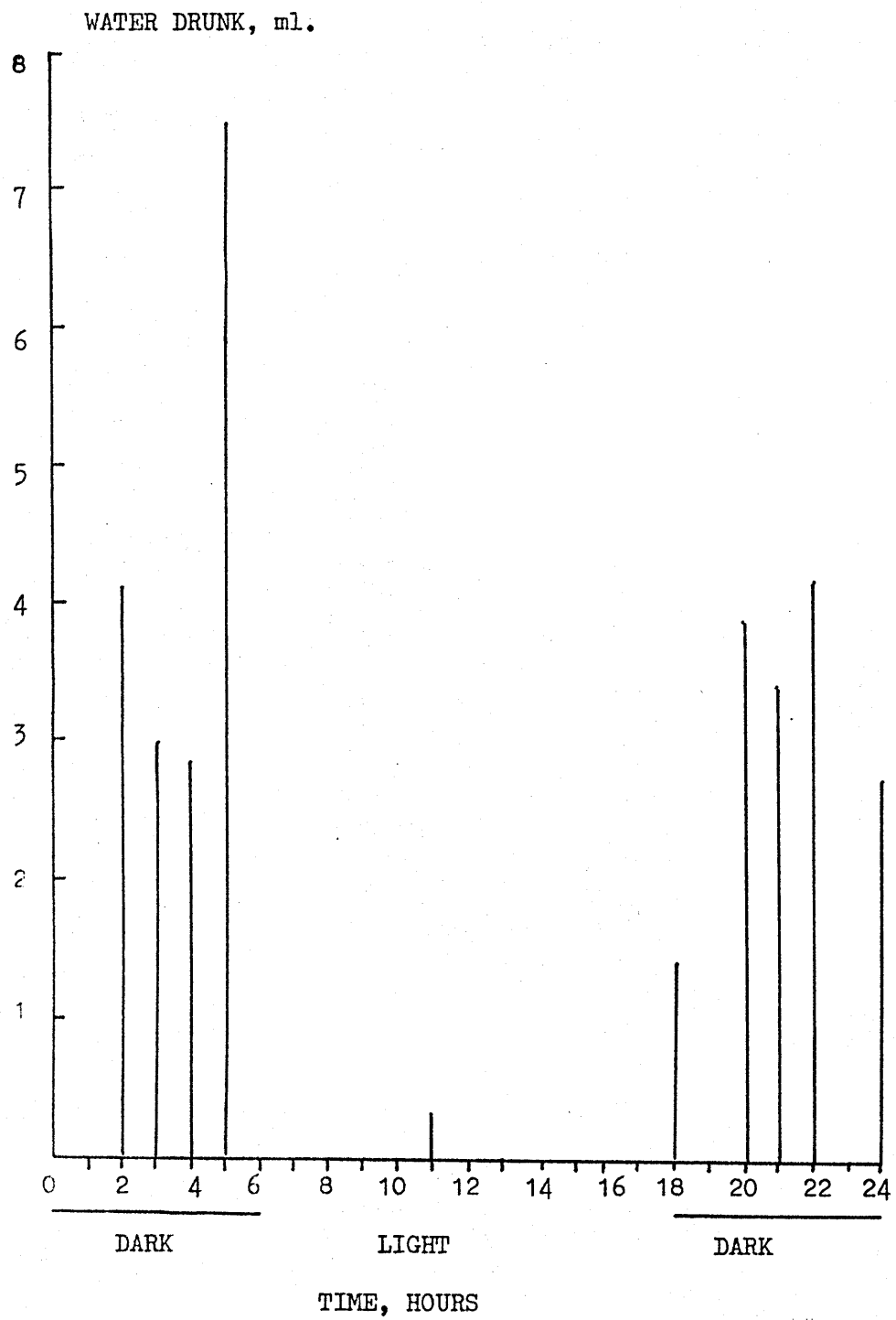


FIGURE 14.1- PREDICTED HOURLY INTAKE, FOOD AD LIB

strong circadian rhythm, which was closely entrained to the pattern of food intake. Thus during the light period, only 1.74 ml of water was drunk; during the equal-length night period, 31.59 ml of water was drunk. The hourly intakes of water are shown in Figure 14.1. Comparison of this with Figure 7.2, which shows meal scheduling, illustrates the close relationship between the two. This has been achieved without any use of oro-pharyngeal feedback signals, and is very similar to published data (e.g. Epstein, 1967; Fitzsimons and LeMagnen, 1969).

On the other hand, there appears to be no similar rhythm of urinary output or insensible water loss. During a normal day, urinary output of water by the simulation is about 24 ml, whilst insensible water loss is about 9 ml. This is in good agreement with published data (e.g. Laszlo and DeWied, 1966; Dicker and Nunn, 1957; Collins, 1978).

The Dynamics of Gastro-intestinal Food in the Normal Animal

As is discussed elsewhere in this volume, the ingestion of food in the 'large rat' simulation is not self-regulated. Rather, a representative feeding pattern was developed, and food presented accordingly. The diet given was just enough to satisfy energy requirements, allowing for energy conversion efficiencies (see elsewhere for a discussion of this, and a description of the system). Nevertheless, it was considered appropriate to study the normal variations of stomach and intestine contents, in order to partially validate the assumptions made during system development. Fortunately, a particularly-well documented paper came to light, permitting a direct comparison between predicted and experimentally observed variations in gastro-intestinal content (Armstrong, Clarke and Coleman, 1978). The results, showing predicted and actual data, are given in Figures 14.2(a) and (b).

Figure 14.2(a) shows the normal circadian variations in stomach content. Within acceptable tolerances, it can be seen that the predicted values are in good agreement with the observed weights.

The same is also the case for circadian variations in intestine content, shown in Figure 14.2(b). It is interesting to note that there is a tendency for both predicted and experimental systems to have a reduced intestinal content at the beginning of the dark period.

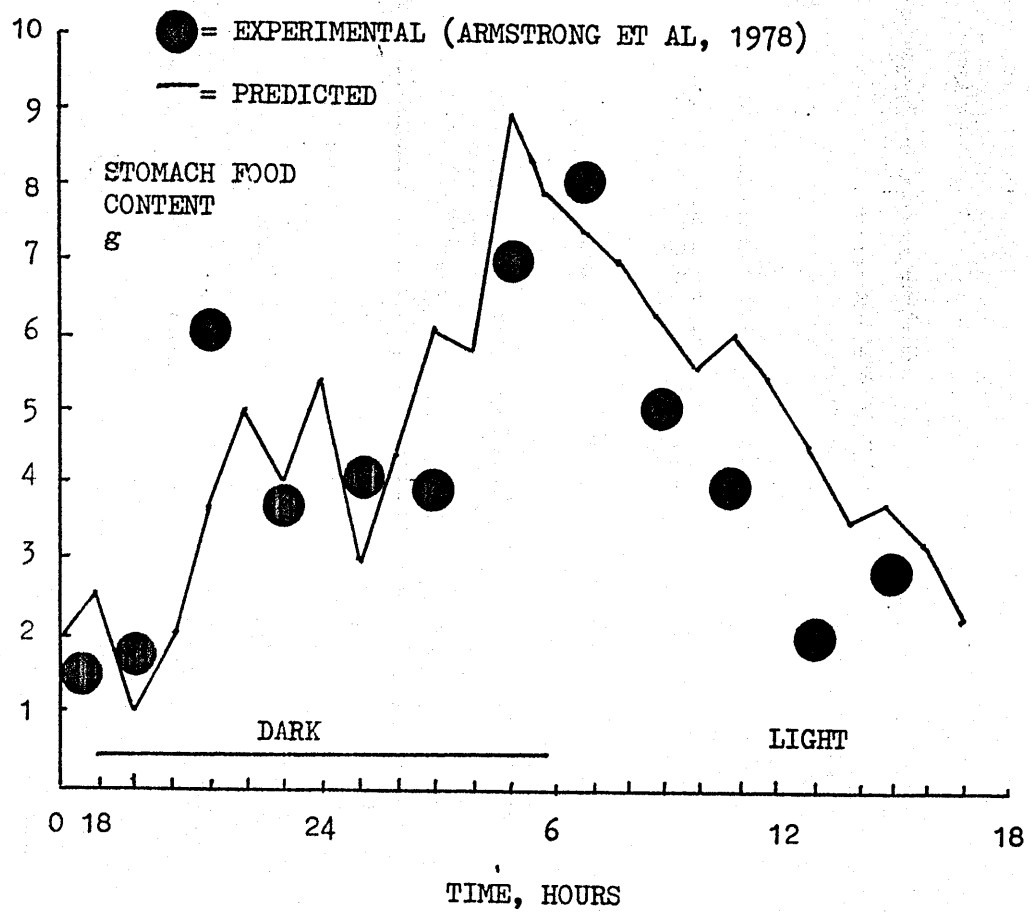


FIGURE 14.2 (a)- STOMACH FOOD CONTENT, ANIMAL FED AD LIB

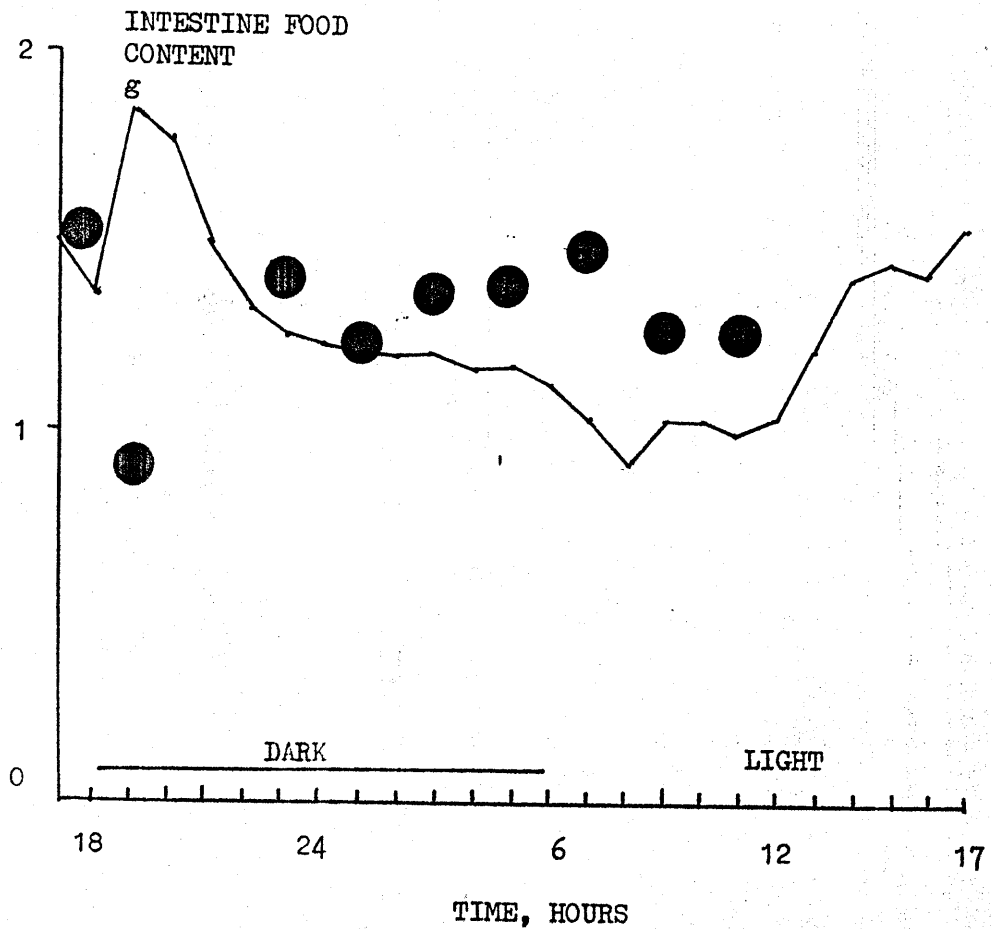


FIGURE 14.2(b)- INTESTINE FOOD CONTENT, ANIMAL FED AD LIB



The Physiological Responses to a Restricted Water Schedule

This simulation aims to investigate the alterations in body fluid profile that occur during deprivation of water, but not food. Verplanck and Hayes (1953) showed that during water deprivation, rats voluntarily reduced their food intake to about 57 % of the 'ad lib' value. Thus this figure was used to determine the intake allowed the simulation (in which food intake is not self-determined). Some results of this simulation are presented below.

Given that the adult rat is normally good at regulating its weight, it can also be assumed that the daily food intake is just adequate to meet its needs. Thus the reduced intake observed during water deprivation will not meet its needs, and body energy stores will be somewhat depleted. In effect, this depletion will mean that the intracellular compartment will be reduced in size, and the water previously held therein will be released to the extracellular spaces. This loss is additional to any losses that occur as a consequence of increases in extracellular osmolality. Previously, it has not been possible to simulate such a situation, due to the lack of any system to represent energy (even one as simple as this). Several predictions and suggestions can be made once one assumes this two-fold intracellular depletion during water deprivation. First, it is predicted that the urinary ratio of Potassium to Sodium will increase, as greater reliance is placed upon intracellular energy reserves, and hypovolemia induces Sodium retention. The rate of Potassium release will not

however be constant, because as time progresses, different energy stores will be depleted, and with them varying proportions of water. Thus glycogen will be the first to be depleted and will release relatively large amounts of water. for the paradoxical diuresis occasionally seen in water-deprived rats. Under many circumstances, the effects of the associated Potassium diuresis may be masked by the high proportions of Potassium normally found in laboratory rat foods. This may well 'carry over' into the deprivation period. Once glycogen has been depleted, the fat reserves will begin to be depleted. These will release much less water, both because per unit mass they contain most energy, and also because they contain relatively little water.

This is not the only factor that operates to change the relative proportions of urinary Potassium and Sodium. Aldosterone, it is predicted, will also have an effect. Increased levels of plasma aldosterone tend to enhance the secretion of Potassium by the renal tubules; the cost of this however is an increased retention of Sodium (which, as is discussed elsewhere, is not entirely disadvantageous). Two factors serve to increase plasma aldosterone. First, the release of intracellular Potassium previously alluded to will do this; second however, there is a 'volemic' stimulus to aldosterone secretion. The precise mechanism by which this operates is not clear, but in this simulation it is linked to plasma levels of angiotensin, the secretion of which is induced by a drop in right atrial pressure (amongst many other factors). The conservation of Sodium on occasions when extracellular volume is depleted is a

sensible response, when one considers that the fluid most likely to be available for restoring the deficit is pure water, which might otherwise produce hyponatremia.

Thus in the first twelve hours of water deprivation with a reduced food intake, the simulation predicted a ratio of urinary Sodium to Potassium of 0.546. This is largely a reflection of the high dietary Potassium. In the second twelve hours, Potassium output remained about the same, but Sodium output dropped dramatically. The greatest change coincided with the depletion of free interstitial fluid; following this the brunt of the fluid loss has to be borne by plasma, and thus the volemic stimulus to aldosterone release increased greatly. In this period, the predicted ratio of urinary Sodium to Potassium decreased to 0.22. There is some evidence that supports these predictions. Mogharabi and Haines (1973) found a urinary ratio of Potassium to Sodium in control rats of 0.89, somewhat more than that predicted; however, this may be attributable to the diet. After between one and two days deprivation of water (with food available), this ratio had dropped, to 0.24. Possibly after this deprivation interval the dietary influence on urinary electrolyte ratios had decreased, thus enabling a greater accuracy of prediction.

Largely in response to an increase in anti-diuretic hormone, predicted urinary output of water also decreased, from an average of .75 ml/hour in the first twelve hours of deprivation to 0.6 ml/hour in the succeeding 12 hours. Since the degree of dehydration is not particularly severe, arterial pressure, and hence glomerular filtration rate did

not decrease. On the other hand, right atrial pressure did, from 3.6 mmHg to 0.93 mmHg. This was largely a consequence of the drop in blood volume from 21.82 ml to 19.01 ml. This corresponded to an increase in haematocrit from 32.1% to 36.8%, which increase of 4.7% compares well with the experimentally observed values of 4% (Rolls, Wood and Rolls, 1980; Blass and Hall, 1976).

Body weight decreased in the simulated rat from 281 g to 256 g, a decrease of 25 g (8.9%). This is in good agreement with the 9% weight loss in 100-day old rats reported by Campbell and Cicala (1962).

Drinking following Water Deprivation- A Study of 'Voluntary Dehydration'

The phenomenon of 'voluntary dehydration' was first referred to by Adolph (1943). It refers to the fact that following a period of deprivation, rats (amongst other animals) do not appear to drink enough water to restore their fluid deficit. It has been studied more recently by Blass and Hall (1976).

Following 24 hours of water deprivation, the simulated animal drank 8.25 ml in the first hour after restoring water. This compares favourably with the experimentally observed intake of about 10 ml (Kutscher, 1972; Blass and Hall, 1976). This similarity means that one can compare the internal hydrational responses of both experimental and simulated rats with some confidence.

The experimental and predicted responses of plasma Sodium and haematocrit are shown in Figure 14.3. It can be seen that in both cases, simulated results are in good agreement <sup>with</sup> those observed in experiment. There is an apparent discrepancy between predicted and experimental haematocrit; this may be due to a difference in interpretation. The simulated haematocrit is determined by red cell/blood volume. That of Blass and Hall (1976) may correspond to red cell/plasma volume. In any event, haematocrit is very variable, and thus this should not be regarded as a serious defect.

It can be seen that following water intake, plasma osmolality drops below normal, indicating that the

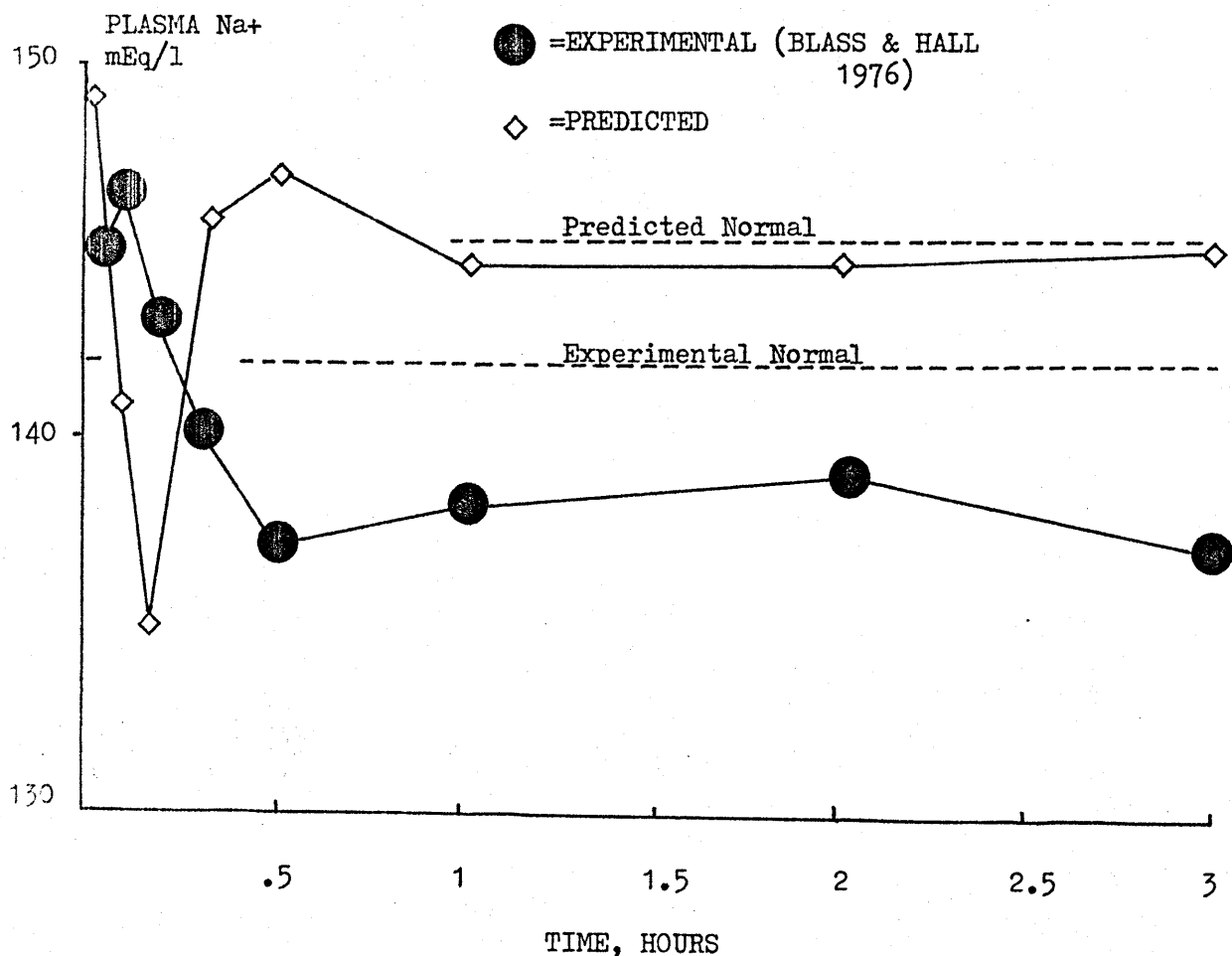


FIGURE 14.3(a)- PLASMA SODIUM CONCENTRATION DURING REHYDRATION FOLLOWING 24 HOUR WATER DEPRIVATION (FOOD AD LIB).

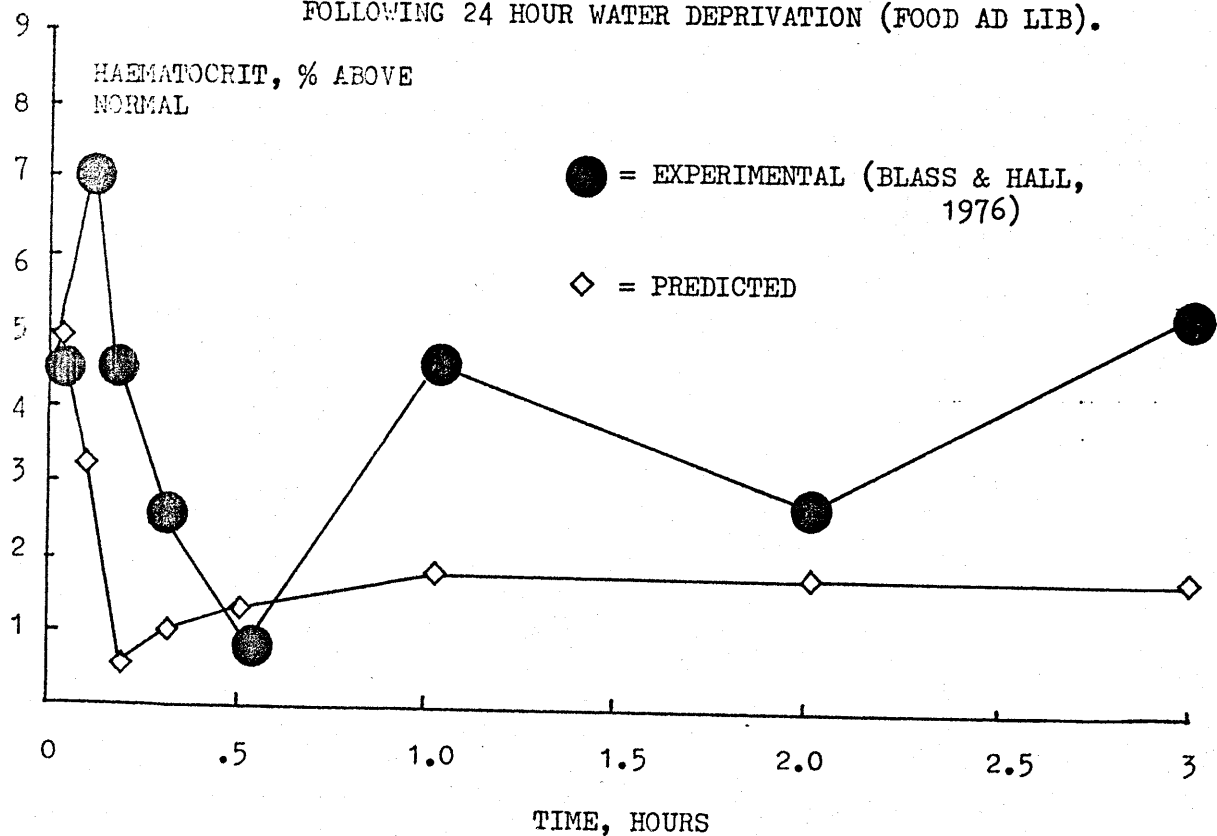


FIGURE 14.3(b)- VARIATION IN HAEMATOCRIT FROM NORMAL DURING REHYDRATION.

conservation of Sodium has not been entirely effective. Similarly, haematocrit drops at first, to near normal values, but then increases again, although not quite to pre-deprivation levels. This trend indicates several stages of water repletion. The initial drop in haematocrit reflects the uptake of water from the gastro-intestinal tract. The subsequent increase shows that the absorbed water is now being distributed throughout the interstitial, and eventually intracellular, compartments.

As is discussed elsewhere in this volume, there are essentially two classes of drinking stimuli; intracellular and extracellular (volemic). One may ask why drinking does not proceed to the point where the original blood volume is restored? One reason for this is the compliance of the vascular system. Over the 24 hours of water deprivation, blood volume decreases. As a consequence, several systems respond to maintain an adequate arterial pressure. Most notable among these is autonomic activity, which increases markedly during the deprivation period from 0.95 to 1.2. Angiotensin also has an effect; this increases in concentration by a factor of about 10. Unfortunately, no data is as yet available to substantiate these predictions. The net result of these stimuli is to increase vascular tone, and reduce the fluid volume necessary to produce a given arterial pressure. Following the restoration of water availability and its subsequent ingestion, these stimuli take time to respond. The vascular tone stays as it was for some considerable time. Thus one factor contributing to the phenomenon of 'voluntary dehydration' is this increase in

vascular tone; in effect the vascular compartment is smaller than it was when dehydration started, and thus less water is needed. Gradually of course, the vascular system will adapt to the new circumstances, but this takes a matter of many hours.

The predicted and experimental net fluid balances of rats following 24 hour fluid deprivation are shown in Figure 14.4. Both indicate that insufficient water is drunk to restore the animals to their pre-deprivation levels of hydration. This has already been partially explained by the reduction in size of the vascular compartment. However, an additional factor can also be discerned. As was mentioned earlier, the energy intake during water deprivation is inadequate, and thus some energy has to be contributed by body energy stores. The contributions (predicted) by each energy store are shown in Table 14.2.

	Reduction	Water Content
Glycogen	0.193 *	.772
Fat	2.755	2.948
Protein	2.45	8.0

Table 14.2 Body energy store depletion (g) and the associated release of water (ml) during 24 hour water deprivation. \* Note that this corresponds to the entire glycogen store.

This shows that the energy deficit induced by water deprivation (albeit a self-imposed deficit) causes a reduction in size of the intracellular compartment. Thus less water need be drunk in order to restore an adequate



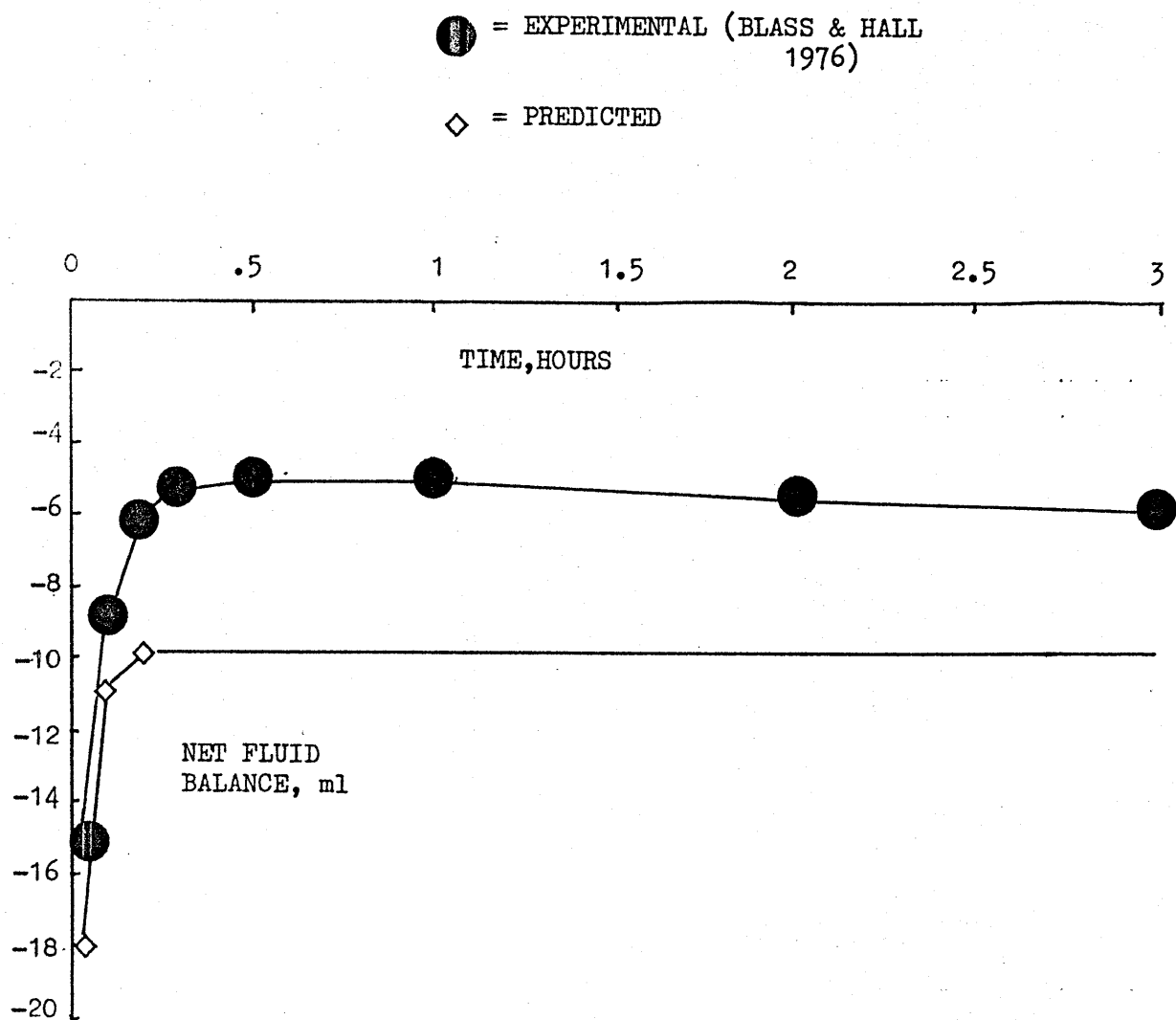


FIGURE 14.4- NET FLUID BALANCE DURING REHYDRATION AFTER 24 HOUR WATER DEPRIVATION (FOOD AD LIB)

● = EXPERIMENTAL (KUTSCHER, 1972)

◇ = PREDICTED

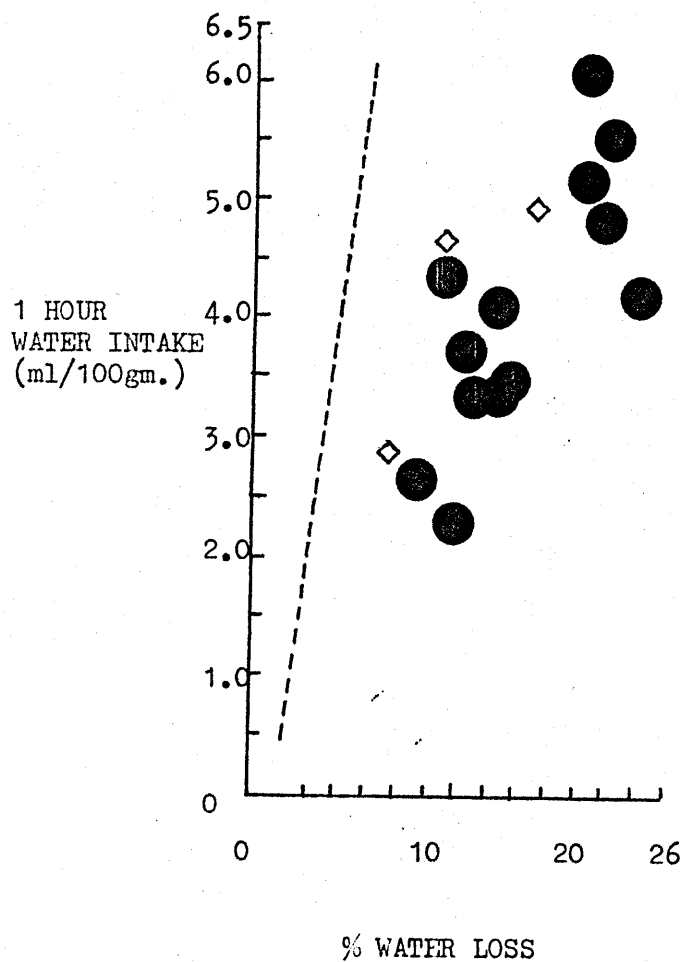


FIGURE 14.5- WATER INTAKE DURING  
1 HOUR AFTER WATER DEPRIVATION  
(FOOD AD LIB) AS A FUNCTION OF  
% WATER LOSS.

osmolality. It is interesting to note that the summed water loss from body reserves (11.72 ml) corresponds roughly to the asymptotic net fluid deficit shown by Blass and Hall (1976) of between 5 and 10 ml. These figures would be closer if the model incorporated some means of modifying its metabolic rate as a consequence of deprivation, as real rats are probably capable of doing. It does appear, on the basis of the original weight loss, that the energy deficit is somewhat less than that calculated. However, it is felt that these factors are the most probable explanation for the phenomenon of 'voluntary dehydration', first observed by Adolph (1943).

Further validation of the hypotheses developed here can be provided by studying the experimental data of Kutscher (1972) and the results predicted by this simulation. Figure 14.5 shows the experimental and predicted drinking responses. It can be seen that there is a good agreement between the two.

The Effects of Blocking Drinking Stimuli on Deprivation-Induced Drinking

There is evidence to suggest that the intracellular stimulus to drinking is mediated by cholinergic receptors (e.g. Miller, 1965). On the other hand, extracellular stimuli appear to be at least partially mediated by receptors sensitive to angiotensin II (see Chapter 7 for a discussion of this topic). These two systems are capable of operating independently of each other. Thus blockade of one does not inhibit drinking elicited by stimulation of the other (Hoffman, Ganten et al, 1978).

The experiment of Hoffman, Ganten et al (1978) was designed to investigate the question of whether these two independent thirst stimuli interact during the control of 'physiological' drinking, and if so, to study the nature of their interaction. Following 48-hour deprivation of water (but not food), they found that neither central angiotensin II nor cholinergic blockade alone significantly affected drinking. However, the simultaneous blocking of both receptors reduced drinking by about 70 per cent. The conclusions reached were that both angiotensin and cholinergic receptors in the brain have a role to play in physiological (i.e. naturally occurring) thirst. Thirst is maintained when either receptor is intact, but reduced when both are inhibited by antagonists. They are independently capable of maintaining thirst. Further evidence for the independent nature of these two systems is provided by Fitzsimons (1979, p.346). Swanson, Marshall et al (1973)

showed that atropine (which blocks cholinergic receptors) does not inhibit drinking caused by angiotensin injected into the same cerebral site. In addition, when carbachol and angiotensin are injected together down the same intracranial cannula, the amount of water drunk is found to be approximately the sum of the amounts drunk after the administration of each dipsogen alone (Fitzsimons, 1979, p.346). The situation appears to be somewhat different in other species of animal.

Rolls and Rolls (1982, p.54) cite Hoffman, Ganten et al (1978) as evidence for a redundancy of drinking mechanisms. In drinking, as in other physiological systems, (so they say) there is a redundancy of mechanisms, so that when one is removed or incapacitated others take over. As the maintenance of fluid balance is essential to the animal, such redundancy could be a great advantage.

As is discussed in greater depth in Chapter 7, incorporating the concept of redundancy into a control system is not easy. It was found that a parsimonious way of achieving this was to dispense with the usual somewhat simplistic notion of straightforward stimulus additivity, and assume that each stimulus also exerts an inhibitory effect on the others. Thus the removal of any one of the stimuli would be partially compensated for by the concomitant removal of its associated inhibition. This somewhat theoretical system is incorporated into the 'large rat' model. The aim of this simulation is to reproduce the circumstances of Hoffman, Ganten et al's (1978) experiment, and study the predicted responses.

The 'experimental conditions' to which the simulation was exposed are as close an approximation as possible to those of Hoffman, Ganten et al (1978). The animal was deprived of water (but not food) for 48 hours. Unfortunately, no data on the food provided, nor the amounts eaten are given. However, the assumption is made here that the animal would eat about 7 grams of food per day. The food provided is, as in other simulations, standard laboratory chow (see Chapter 7 for its analysis).

About 10 minutes before water was made available, one or both of the variables INIC or INANG was reduced to zero. The former variable represents the intracellular stimulus to drinking, which in turn is derived from intracellular energy state (see Chapter 15). This therefore simulates the intracerebral infusion of atropine sulphate. The latter variable represents the stimulus to drinking arising from angiotensin II concentration, which plays an important role in mediating extracellular-induced drinking. Reducing this to zero therefore simulates the effect of intracerebral saralasin, an angiotensin II blocker. The control simulation permitted no reduction in either of the two stimuli, but was otherwise as described above. In each case fluid intake was studied over a period of two hours, data being made available at 20, 60, 90 and 120 minutes.

The data produced by the simulation are shown in Table 14.3. The results of Hoffman, Ganten et al (1978) are also shown, for comparison. It can be seen that generally there is a very good relationship between the predicted and experimental consequences of atropine and saralasin

infusions.

	Intake (ml, 1 hr period)	
	Predicted	Experimental
Control	13.56	13.2
Ang. blocked	13.56	12.0
Intrac. blocked	13.56	10.6
Both blocked	0.0	4.8 *

Table 14.3 Predicted and actual water intakes after blockage of one or two independent drinking stimuli. \* Significantly different from other experimental groups ( $p < 0.001$ )

As predicted, there is no difference between the single-substance infusion cases and the control, in which no stimuli were blocked. The predicted response to blockade of both stimuli is however, a little over-dramatic; no drinking at all was observed.

Thus far, the predicted results appear to fit well the experimental findings. They corroborate the arguments of Rolls and Rolls (1982) with respect to a redundancy of drinking mechanisms, and also those presented in Chapter 7 regarding an additive/inhibitory interaction of drinking stimuli. However, despite these glad tidings, a note of caution must be sounded. Closer examination of the model's responses has indicated an alternative explanation, which is compatible with both the additive/inhibitory system described here, and the traditional simple additive system.

Drinking is normally considered to be initiated

whenever the summed stimuli exceed a given value, or threshold. Thus drinking is an 'all-or-nothing' affair. The rate of drinking in the rat is relatively constant (see Chapter 7), and does not reflect the strength of motivation.

The capacity of the gastro-intestinal tract to hold and absorb fluid is limited. Following a prolonged period of deprivation the motivation to drink is very strong, and the animal will ingest water as rapidly as possible. Under these circumstances, in the short term the limiting factor on fluid intake may be the gastro-intestinal tract's capacity, rather than the motivational strength.

After 48 hours of water deprivation, the summed effect of the three stimuli is naturally to induce rapid drinking. The gut soon fills with water, and the distension thus produced inhibits further drinking (Adolph, 1950), despite the animal still being dehydrated. Such a period of deprivation (48 hours) is severe, and thus the abolition of any one drinking stimulus may still cause so much ingestion of water as to again exceed the gut's capacity. Only when two stimuli are blocked will the gut cease to be a short-term limiting factor. Thus the appearance given will be of an animal where abolition of any one stimulus does not affect deprivation-induced drinking. Such an explanation is entirely compatible with either an additive or additive/inhibitory system. Consequently, one should be somewhat guarded when citing such an experiment as evidence for the type of system described here.

It is often stated that one of the best tests of a simulation is its ability to provide counter-intuitive



predictions; it is no great achievement for a simulation to tell one something one already knows. The alternative explanation for the findings of Hoffman, Ganten et al (1978) suggested by the simulation certainly falls into this category. However, one must admit that it would be a little more encouraging if the consequence of one such counter-intuitive prediction was not to remove potential support for the author's own theories. At least one can be consoled by the fact that it does not directly disprove the additive/inhibitory theory; it merely means that the findings previously cited as support are in reality inconclusive.

The Effects of Caval Ligation on Drinking in Normal and Nephrectomised Rats

As is discussed elsewhere in this volume, the atria of the heart and the walls of the vena cava contain many receptors, the function of which is to indicate to the brain information regarding the degree of filling of the cardiovascular system. Such receptors have been implicated in a number of roles relevant to water homeostasis, such as anti-diuretic hormone secretion (see Chapter 12) and drinking (see Fitzsimons, 1979, p.213). Fitzsimons (1964, 1969) showed that complete ligation of the abdominal inferior vena cava above the renal veins, but below the hepatic and right adrenal veins is an effective stimulus to drinking in the rat. The ligated vein normally conveys about one third of the venous return to the heart, and thus its abrupt closure causes a dramatic drop in both right atrial and arterial pressures. The latter, being better defended by the autonomic system, rapidly recovers to nearly its normal value, but right atrial pressure remains at a low level.

The effect of ligating this vein is to increase the venous resistance to blood flow, and this can easily be simulated by the 'large rat' simulation, due to the completeness with which the cardiovascular system is represented. To realistically simulate such a phenomenon as this would permit a close theoretical analysis of the hormonal, autonomic and renal responses elicited by caval ligation.

The results of this and other caval ligation

experiments are shown in Table 14.4. The simulated data are presented alongside the experimental data of Fitzsimons (1969), for comparison.

Group	Water drunk (ml/100g b.w.)	Urine volume (ml/100g b.w.)
Sham operated (Control)	0.0 (0.43)	1.53 (0.86)
Caval ligation	5.15 (4.2)	0.415 (0.24)
Caval ligation, nephrectomised animal	1.89 (1.6)	-- --

Table 14.4 Drinking and Excretion in the 6 hours following caval ligation. Experimental data in parentheses.

It can be seen that there is a reasonable agreement between the predicted and experimentally observed data. Such drinking is, of course, entirely inappropriate. To ingest such quantities of water at a time when urinary output is very low results in a decrease in plasma osmolality. Water intake and plasma levels of anti-diuretic hormone (ADH) are increased in spite of a fall in plasma osmolality and an increase in vascular volume. Thus, as Thrasher, Moore-Gillon et al (1983) point out, chronic caval constriction causes a profound primary disturbance in mechanisms regulating water balance, which can contribute to the formation of edema fluid. Their experiments were unfortunately conducted on dogs, so one cannot directly compare their results with those of this simulation.

Of particular interest are the responses given by a 'nephrectomised' animal. In the simulation this effect was achieved by reducing all urinary outputs and glomerular filtration rates to zero. Incidentally, this operation also had the effect of significantly increasing the half-life of most hormones. Because the kidneys are the body's main source of renin, renin secretion rate was also reduced to zero. In effect, this removed the renin-angiotensin system, and thus deprived the animal of an important means of controlling drinking and cardiovascular tone. To ensure that the 'nephrectomised' simulation was in all other respects as similar as possible to the normal simulation, these interventions were carried out one hour before caval ligation (i.e. venous resistance was increased). This allowed plasma angiotensin levels to fall to very low levels, but ensured that the body fluid profile did not alter significantly.

It is interesting to note that nephrectomy does drastically reduce the amount of water drunk following caval ligation, but it does not completely abolish it. This is due to the influence of a third drinking controller, determined by atrial stretch receptors (see Chapter 7). The dramatic reduction in right atrial pressure induced by caval ligation stimulates these receptors sufficiently strongly to cause some drinking, although not as much as would be caused by the combined stimuli of the renin-angiotensin system and atrial receptors. Indeed, some would argue that the renin-angiotensin system is not essential either in deprivation- or caval ligation-induced drinking (Lee, Thrasher and

Ramsay, 1982). They base their arguments on the failure of cerebral saralasin (an angiotensin II blocker) to significantly reduce drinking caused by either of these two conditions. Such however, is not the finding suggested by the current simulation. It is possible that their results represent another example of 'stimulus redundancy', discussed elsewhere in this Chapter.

Closer study of the simulations presented here enable one to form some hypotheses as to the causes of the reduced urinary output following caval ligation. First, the drop in arterial pressure caused by this intervention results in a reduction of renal perfusion pressure, and hence glomerular filtration rate. This reduction is further exacerbated by renal arteriolar constriction, due to the increased levels of circulating angiotensin.

As is discussed elsewhere (Chapter 12), a major determinant of anti-diuretic hormone (ADH) release is atrial pressure, mediated by stretch receptors. Thus perhaps it is not surprising that following caval ligation, ADH concentrations increase enormously, from a normal of about 3 pg/ml to about 100 pg/ml. For comparison, 24 hour water deprivation increases plasma ADH to about 17 pg/ml in the rat (Dunn et al, 1973). This greatly increases the proportion of glomerular filtrate that is reabsorbed, and thus further reduces urinary output of water.

At such high concentrations, it is quite possible that ADH also exerts some pressor effects on the cardiovascular system, and thus the consequences of caval ligation may be even more complex than appear at first sight. Certainly,

ADH has been studied for its potential role in regulation of cardiovascular tone (Schwartz and Reid, 1983), at least in dogs. In addition, as is discussed in Chapter 10, the renin-angiotensin and ADH systems do not operate in isolation; an increase in ADH influences angiotensin levels, and vice versa. It would be interesting to examine this further, to see whether oscillation of either ADH or angiotensin levels takes place during caval ligation.

CHAPTER 15The Nature of the Intracellular Stimulus to ThirstIntroduction

The aim of this Chapter is to study, in terms of control systems, the behaviour of the cellular compartment, or to be more precise, the behaviour of the small number of cells elected to act as representatives of the intracellular compartment. Although drinking induced by cellular dehydration has long been regarded as a valid phenomenon, only a few actual correlates of dehydration have ever been postulated as initiators of this behaviour. Currently, as is discussed elsewhere in this volume, theorists tend to fall into one of two camps.

Gilman (1937) showed that a critical stimulus for drinking following dehydration is the loss of water from the cells. The infusion of hypertonic saline withdraws fluid from the cells by osmosis, as the Sodium is excluded from the intracellular compartment. This induces drinking. Urea however, can cross the cellular membrane. Thus infusion of urea in such concentrations as to increase the osmolarity of the extracellular fluid by an equal degree to that achieved by saline infusion will not induce drinking, because the increase in osmolality is equal in both intracellular and extracellular compartments. Since no concentration gradients are created, there is no intracellular dehydration.

As a consequence of this historic experiment, the majority of theorists hold the view that intracellular drinking is mediated by the dehydration of 'osmoreceptors',

sited within the brain (Wood, Rolls and Ramsay 1977), sensitive to variations in the tonicity of their immediate environs. The actual stimulus normally suggested as the initiator of intracellular-induced drinking is a reduction in cellular volume (Gilman, 1937). Most theorists would regard themselves as belonging to this group.

There is however a smaller, vociferous group in Sweden, who stress the belief that the relevant receptors respond not to variations in tonicity per se, but variations in cerebro-spinal fluid Sodium concentration (Andersson and Olsson, 1973; Andersson, 1978). The main proponent of this theory is Bengt Andersson, who showed in 1953 that injections of hypertonic Sodium Chloride solution directly into the hypothalamus causes drinking in the goat (Andersson, 1953).

On the basis of current experimental data, it is not possible to determine which, if either, of the two theories is correct. An apparently critical test to decide between the two is to apply an osmotically active substance other than Sodium, and determine whether drinking follows. Thus Blass and Epstein (1971) and Peck and Novin (1971) found that the application of sucrose directly to the central osmoreceptors in the hypothalamus stimulates drinking, both in the rat and the rabbit. \* In an additional test of Andersson's theory, it was found that drinking does not correlate well with the concentration of Sodium in the

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\* Sucrose is a disaccharide, and cannot be taken up by cells. Glucose however, is a monosaccharide and thus is readily transported across the cell membrane.



cerebro-spinal fluid (Epstein, 1978). Rather, drinking was related to the withdrawal of fluid from the cells, at least during ventricular infusions of Sodium or sucrose (Thrasher, Jones et al, 1980; Ramsay, Thrasher and Keil, 1980).

All this tends to lend weight to the argument originally stated by Gilman (1937), that dehydration of cells is the crucial stimulus subserving thirst, rather than Sodium concentration or absolute osmotic pressure. One could argue of course that under normal circumstances, the question of which theory is correct is not relevant. In practice, plasma Sodium concentration and plasma osmolality are very highly correlated, so both are good indicators of the degree of cellular dehydration (Wood, Rolls and Ramsay, 1977). However, as will be argued later in this Chapter, the controversy created by the proponents of these two theories has rather polarised attitudes, and perhaps one can begin to elucidate the situation by looking more closely at what is likely to happen within the cell exposed to hypertonic stress. Furthermore, as Rolls and Rolls (1982) pointed out, cellular dehydration accounts for a large fraction of normal drinking. Thus, the discussion presented here is not of mere academic interest. It is hoped that the model described will help resolve differences, and explain experimental findings largely ignored to date.

Although many of the arguments presented here may apply to the majority of body cells that comprise the intracellular compartment, the model developed in this Chapter should be regarded as a theoretical study of the hypothalamic osmoreceptors, termed elsewhere the 'neural

intracellular compartment'. The unique position of these receptors, in this densely vascularised part of the brain, has been discussed elsewhere. Briefly however, by occupying such a position, they are able to act as 'early warning detectors', indicating not the current state of the intracellular compartment, but the probable state in the near future.

#### The Development and Description of the Model

As is discussed elsewhere, the intracellular compartment maintains a high concentration of Potassium ions (relative to plasma levels). The presence of these large quantities of positive ions serves to counteract the electronegative charges held by the intracellular proteins. Sodium ions are excluded from the cells, and thus concentrations of this ion are lower than plasma.

The mechanism fundamentally responsible for maintaining this situation is generally referred to as the Sodium/Potassium (Na/K) pump. It is of critical importance in the regulation of cellular volume (MacKnight and Leaf, 1977). The Na/K pump, the energy for which is provided by adenosine triphosphate (ATP), is basically an 'exchange pump', in which extracellular Potassium ions are transported into the cell, in exchange for intracellular Sodium ions. However, the Na/K pump displays a curious stoichiometry. Three Sodium ions are pumped from the inside and two Potassium ions from the outside of a cell for each molecule of ATP utilised (Metzler, 1977, p.270). The pumping of Sodium and Potassium ions is one of the most important

energy-requiring activities of cells. In resting muscles, it can account for half the ATP utilization; in nerve cells, it can utilise a much larger fraction, up to 90 per cent. The supply of ATP necessary for this process, and hence the regulation of cellular volume, is maintained by the glycolysis of glucose, and the subsequent subjection of the resulting acetyl groups to the citric acid, or Krebs, cycle. The oxidative degradation of glucose is thus a gradual process, forming 38 mols of ATP for every mol of glucose. In experimental conditions, the overall efficiency of conversion for glucose to ATP is 29 per cent, the remainder being lost as heat (Guyton, 1976, p.908; Metzler, 1977) Glucose, derived ultimately from digested food, is transported across the cell membrane by a process of facilitated diffusion. The direction of flow is down the concentration gradient, so energy is not required for its importation into the cell, but the glucose molecule is too large to be able to diffuse freely across the cell membrane. Consequently each molecule has to become attached to a 'carrier' molecule, embedded in the cellular membrane, before it can be transported across (Guyton, 1976, p.905). The specificity of this carrier molecule explains why monosaccharides such as glucose can be readily transported and utilised, whilst the closely-related disaccharides cannot. A characteristic of facilitated diffusion transport systems such as this is that they exhibit clearly-defined maximum transport rates, for any given permeability value of the cellular membrane. Thus transport rate will increase linearly with plasma concentration, but only up to the point

where all the available transport sites are currently utilised. A further increase in plasma glucose will elicit no further improvement in transport rates. The only means by which more glucose can be delivered to the intracellular processes of glycolysis and the citric acid cycle is by increasing the permeability of the cellular membrane to glucose, i.e. either providing more carrier sites or making the existing ones more active. In the muscle, and hepatic cells (amongst others), this is achieved by the hormone insulin. An increase in the concentration of this large polypeptide stimulates the uptake of glucose from the plasma greatly- or rather it eases the transfer of glucose for its subsequent utilisation by intracellular processes, such as its conversion to energy stores. Insulin is particularly effective in skeletal muscle and adipose tissue; in the human, these two alone make up about 65 per cent of total body weight. In addition, insulin enhances glucose transport into the heart and some smooth muscle organs, such as the uterus (human data; Guyton, 1976, p.1038). This system, permitting the creation of energy reserves during times of plenty, and releasing them during periods of shortage from most of the body, permits plasma glucose levels to be maintained very accurately. This is just as well, for under normal circumstances the brain is capable of utilising only glucose for its energy requirements; furthermore it is particularly sensitive to any decreases in plasma glucose concentration. For this reason, glucose is 'spared' for use by the central nervous system during prolonged periods of food deprivation, with the rest of the body 'making do' with

alternative energy substrates, such as ketone bodies (Davidson, Passmore, Brock and Truswell, 1975).

Insulin does not promote the uptake of glucose by the central nervous system. Thus considering the proportion of the nerve cell's energy that has to be expended in order to maintain the Na/K pump, the lack of flexibility imposed upon the system by the negligible effect of insulin, and the sensitivity of the brain to reductions in plasma glucose levels, it is easy to foresee circumstances in which the rate of energy supply is a 'rate limiting factor' on the performance of the Na/K pump. It is further felt that the rate-limiting effect of an inadequate energy supply can make itself felt under physiological conditions, and is not a phenomenon to be observed only in the clinically ill patient. Severe symptoms of 'insulin shock' can occur when the plasma concentration of glucose has fallen by as little as 50 per cent, resulting in a loss of consciousness. In this state, if treatment is not effected immediately, permanent damage to the neuronal cells will result.

Perhaps it should be pointed out that the critical factor is not really plasma glucose concentration, but the intracellular availability for conversion to ATP. The result of decreases in plasma concentration of glucose is to reduce intracellular availability because the concentration gradient across the cellular membrane, and hence the rate of flow, is reduced.

All this serves to emphasise that the brain is dependent on a minute-to-minute supply of glucose. It contains essentially no fuel reserves of either glycogen or

triacylglycerols (Lehninger, 1975, p.838), and can only utilise glucose. The human brain uses 20 per cent or more of the total Oxygen consumed by the resting adult, and of this perhaps two thirds is used to maintain the membrane potential by means of the Na/K pump.

It is essential for optimum performance of the nerve cell that adequate concentrations of intracellular Potassium be maintained. Relatively high concentrations of internal Potassium are required for several processes vital to the function of the cell. These include protein biosynthesis by ribosomes, plus of course maintenance of the membrane potential in excitable cells (Lehninger, 1975). However, considering the theory being developed here, it is particularly relevant to note that Potassium is required in the glycolytic sequence for maximal activity of pyruvate kinase. This is a vital stage in the oxidation of glucose to form ATP (Lehninger, 1975, p.431). Thus it is conceivable that under some circumstances the cell could become caught in a 'vicious circle', in which the shortage of ATP caused by lack of Potassium results in further losses of Potassium down the concentration gradient and into the extracellular spaces.

Bia and DeFronzo (1981) reviewed 'extrarenal Potassium homeostasis'. Although chronic Potassium homeostasis is primarily regulated by the kidneys, acute Potassium tolerance is largely determined by body tissues. Following an acute Potassium load, only about 50 per cent is excreted by the kidneys in the first 6 hours. Of this remaining

infusate, over 80 per cent is translocated into cells. This provides the primary defence against hyperkalemia, which is a potentially lethal situation. This is true whether the Potassium is given orally (Gonick, Kleeman, et. al., 1971) or intravenously, and has been observed in humans (DeFronzo, Taufield, et al, 1979), dogs (DeFronzo, Sherwin, et al, 1978) and rats (DeFronzo, Lee, et al, 1980).

The tissues involved in this aspect of extra-renal Potassium homeostasis appear to be primarily the deep muscle and adipose tissues (Zierler and Rabinowitz, 1964- man). It may well be significant that these are exactly the tissues involved in glucose uptake following increases in plasma insulin concentration. There is much evidence to suggest that insulin has an important role to play in both the metabolism of Potassium and glucose. The evidence for involvement in glucose is discussed briefly elsewhere in this Chapter, and may be examined in greater detail in any standard physiology text, e.g. Guyton (1976).

The importance of insulin in the disposal of a Potassium load has been demonstrated by many investigators, for example Davidson and Hiatt (1972) (dogs) and Dluhy, Axelrod and Williams (1972) (humans). In addition, it appears that insulin forms part of a negative feedback loop involved in Potassium homeostasis. Potassium Chloride infusion into dogs at physiological doses causes a two- to three-fold increase in peripheral insulin levels, in both man and dog (references as preceding). Inhibition of insulin secretion by infusion of somatostatin greatly reduces the animal's tolerance to Potassium Chloride

infusions (DeFronzo, Sherwin, et al, 1978- dog).

Thus one can begin to see that the metabolism of inorganic ions, glucose and insulin is closely related. The links appear to be even stronger when one considers the finding that the active uptake of glucose by tissues capable of doing so (mostly gut and hepatic cells) is dependent upon the presence of Sodium ions. The two appear to be inextricably linked in this process.

By what means is excess extracellular Potassium transported into the cell? As has been discussed earlier in this Chapter, the Potassium has to be transported across the cell membrane against a concentration gradient, 'uphill' as it were. This means that energy is required, and the most likely substrate for this energy is, in the first instance, ATP. Perhaps not surprisingly, the most likely mechanism responsible for transport of these excess electrolytes is the Na/K pump. It has been demonstrated many times that this pump is disabled by a group of chemicals known as 'cardiac glycosides', amongst which the most commonly used is ouabain (MacKnight and Leaf, 1977). Yet despite initial swelling (due to the influx of extracellular Sodium and Chloride ions) following ouabain administration, the cells are not destroyed. They do appear to be able to maintain cellular volume, albeit with considerably less accuracy than before. This regulation is however suppressed by isolating tissues in conditions that prevent metabolism. Restoration of metabolism similarly results in the restoration of cellular volume regulation (Mudge, 1951). This does tend to suggest the presence of additional active transport systems,



capable of handling Potassium and Sodium. The nature of these additional systems is unclear, but they obviously do not operate by the same mechanism as the Na/K pump. Perhaps they operate as relatively energy-expensive systems for use 'in emergency only', whilst the Na/K pump affords a cheaper means of transport, suitable for most occasions. Certainly, on examination of the model presented here, the 'emergency only' transport mechanisms appeared essential to the normal operation of the cell, due to the unusual stoichiometry of the Na/K pump making equilibrium by this means alone very difficult to achieve.

It was pointed out earlier that insulin does not affect glucose uptake by neurons, despite its dramatic effect on other tissues. In addition, it is probably incapable of crossing the blood-brain barrier, on account of the relatively high molecular weight of insulin; it's too big to get through. Therefore it seems reasonable to suspect that under normal circumstances insulin is also not available to assist in the uptake of Potassium by neurons. Again one is faced with the probability that the welfare of other body tissues is sacrificed in order to maintain the equilibrium of the central nervous system. Indeed, this system even has its own unique means of maintaining normal cellular volume when surrounded by chronically hyper- or hypo-osmotic media (Pollock and Arief, 1980). This paper is discussed elsewhere in this volume, but briefly it appears that following an increase in medium osmolality, and subsequent neuronal shrinkage, the cells start manufacturing proteins that exert an osmotic pressure, and thus restore normal

volume. This finding alone should point out the inadequacy of the 'cellular shrinkage' theory of intracellular- induced drinking, which would predict the disappearance of the drinking stimulus after a period of about 24 hours, due to the restoration of cellular volume. To date, no evidence has come to light indicating the validity of this somewhat unlikely event.

However, it is extremely common, even normal, for every nerve cell to be faced with circumstances in which the extracellular concentration of Potassium in the immediate locality is well above normal. As part of the process of a cell 'firing', the cell membrane's permeability to Potassium increases sharply in the locality of the action potential, resulting in a loss of this ion from the intra- to the extra- cellular compartment. Considering the importance of Potassium both to the maintenance of the resting potential and the supply of energy (via glycolysis and the citric acid cycle) for the Na/K pump, it is obviously important to regain this lost Potassium as quickly as possible.

There is also much evidence to suggest that high extracellular Potassium concentrations are just as detrimental to the activity of the central nervous system as are low intracellular concentrations. Although glial cells nearby the neurons are capable of acting as 'short term reserves' (Kuffler, Nichols and Orkand, 1966), taking up Potassium released by the neurons, there is still a dramatic increase in Potassium ion concentration in the external space. This phenomenon was first observed by Frankenhaeuser and Hodgkin (1956) in the squid axon. During a train of

nerve impulses Potassium ions accumulate externally; the final values obtained were directly proportional to the rate of firing. (This subject is reviewed by Adelman and Palti, 1972). The build-up of extracellular Potassium can easily produce hypersensitivity of the neurons (Nicholls and Baylor, 1968). Paradoxically, another example of a neural effect which probably results from Potassium ion accumulation is 'spreading depression'. In this state, the extracellular Potassium concentration increases by up to 8 times (Brinley, Kandell and Marshall, 1960). Similarly, Bures, Buresova and Krivanek (1960) reviewed the literature pertaining to substances that experimentally induce spreading cortical depression. One of these agents is Potassium Chloride. This review also gave support to the finding that the efflux of Potassium from the cortical surface increased during spreading depression. Perhaps of particular significance to the argument being developed here is that brain glycogen and glucose are depleted by about 30 per cent, whereas brain lactic acid increases by about 100 per cent. Both these findings indicate that a severe strain is being placed on the available energy reserves. Obviously, the most effective means of recovering this lost Potassium would be via the Na/K pump, or perhaps by one of the unspecified active transport pathways discussed earlier. Whichever may play the greater role, it would presumably be beneficial for the central nervous system as a whole if the relevant active transport processes could accelerate following a series of action potentials. The most obvious means by which this could be achieved would be to link

transport rate to extracellular Potassium concentration. That such mechanisms have been shown to exist in other types of cell makes this quite likely. However, more direct evidence exists. Potassium influx and Sodium efflux rates in erythrocytes respond in a sigmoidal manner to extracellular Potassium (Priestland and Whittam, 1968). Ion transport in non-myelinated nerve is also positively related to extracellular Potassium, although the function in this case is hyperbolic (Rang and Ritchie, 1968). On the other hand, glycoside-sensitive (i.e. Na/K pump mediated) transport rates in squid giant axons show a sigmoidal relationship to external Potassium (Baker, Blaustein, et al, 1969). The reasons for these differences are not clear.

Thus one is forced to the conclusion that extracellular Potassium is a rate-limiting factor in the active, energy-utilising, transport of electrolytes.

To summarise, two crucial rate-limiting factors in the neuronal active transport of Sodium and Potassium have now been postulated. The first is intracellular energy substrate availability. In the first instance this means ATP, but the argument is intended to apply just as strongly to its precursor, intracellular glucose. The second postulated rate-limiting factor is extracellular Potassium concentration. Furthermore, it is suggested that these rate-limiting factors are capable of exerting an influence under normal physiological conditions, not just under the wider range of experimentally inducible conditions.

There is no doubt that these are not the only rate-limiting factors in this complex process. Glynn and Karlisch

(1975) have shown that the rate of ATP hydrolysis by the Na/K pump is linearly, and positively, related to intracellular Sodium concentration over a nearly physiological range. However, it is these two factors upon which greatest emphasis shall be placed in this particular model. It is felt that the model not only provides a better explanation for the 'popular' initiators of intracellular-induced drinking, but also enables incorporation for the first time of many studies previously ignored, or held to be interesting, but outside the current frame of reference. As an additional bonus, it also offers the exciting possibility of linking, in motivational terms, the areas of both drinking and feeding.

For the last twenty years or so, there has been much debate about which of the two current theories about the nature of intracellular-induced drinking is correct. More heat than light has been created by the not always friendly rivalry between the two camps, and one gets the impression that little, if any, progress has been made. In fact, the situation may even have worsened. The emphasis of the Swedish researchers, especially Bengt Andersson, upon central Sodium receptors, and the sometimes vitriolic responses of those who wish to dissent, has focussed attention on virtually one phenomenon alone- drinking induced by infusion of hypertonic Sodium Chloride. There is a massive body of information relating either cerebral or intravenous (and virtually intra-everywhere else) infusion of hypertonic saline to drinking. Most discussions as to the relative merits of the two opposing theories (e.g. Rolls and

Rolls, 1982) tend to concentrate on this phenomenon, despite it being unable to differentiate between them. Generally, the conclusion reached is that there is more evidence in favour of the 'osmoreceptor' theory, because of its ability to explain sucrose or mannitol-induced drinking. Yet there lies in the literature large numbers of reliable experiments that neither is capable of explaining. These are generally brushed aside. For example, the conventional wisdom is that infusion of Potassium salts fails to induce drinking. In many circumstances, this appears to be the case. In an early experiment, Gamble, Putnam and McKhann (1929) studied the effects on drinking of various salts added to the diet. Sodium Chloride was the most effective stimulus to drinking; Potassium Chloride on the other hand was not very effective. These experiments were later extended by Gamble, McKhann, Butler and Tuthill (1934). In a similar experiment, Arden (1934) added Sodium and Potassium salts to the diet of humans, and studied their dipsogenic effects. Neither Potassium Chloride, nor bicarbonate, were effective in producing drinking.

Such findings are as one would have predicted with the 'osmoreceptor theory', for infusion of Potassium induces cellular swelling, a finding hardly compatible with the induction of drinking. However, the position becomes a little less certain when the Potassium salts are infused intravenously. Certainly, Potassium infusion seems to elicit little drinking in the intact iguana (Fitzsimons and Kaufman, 1977). However, despite the possible contribution of species differences, Arden (1934) found that although

Potassium salts did not appear to induce drinking, they were more effective diuretics than any Sodium salts. This raises the possibility that under normal circumstances, any drinking responses following Potassium infusion may be especially 'blunted' by their rapid renal clearance from the circulation. Such a 'blunting' has already been observed by Fitzsimons (1961) with regard to Sodium, and one can only assume the effect would be greater in the case of Potassium. Indeed, Fitzsimons (1961) infused Potassium salts into nephrectomised rats, with surprising results. In this case, the normal renal contribution to Potassium removal is not present. As the author wrote, 'Potassium salts were unexpectedly effective in causing nephrectomised rats to drink, even when immediate access to drinking water was prevented' (Fitzsimons, 1961, p.573). This obviously is somewhat difficult to reconcile with current theories of intracellular drinking.

In addition this paper gives some fascinating hints both about the dangers of hyperkalemia, and the effectiveness of the systems for extrarenal Potassium homeostasis, discussed earlier (Bia and DeFronzo, 1981). The toxicity of the Potassium infusions was very much greater than the Sodium salts. Injections had to be given slowly, and in divided doses. Despite these precautions however symptoms of toxicity usually manifested themselves. These consisted of irregular muscular movements, temporary paralysis and heart irregularities. Yet recovery was apparently complete after only five to ten minutes; the rats would then start to drink. This recovery is presumably a

consequence of the induced absorption of Potassium by muscle and adipose tissues, discussed earlier; there is no possibility of renal clearance. Whilst this obviously is of crucial importance to the animal, it must also be regarded as an additional 'blunting' of the potential Potassium-related stimulus to drinking. The fact that despite these intervening buffer mechanisms Potassium can induce any drinking at all is particularly striking, considering the conventional wisdom that Potassium salts are unimportant in drinking regulation.

The critical test is to circumvent these buffer mechanisms, both renal and extrarenal, and apply Potassium salts directly to the neurons considered responsible for eliciting intracellular-induced drinking. Fortunately, such an experiment has been done. Olsson (1969) slowly infused Potassium Chloride solutions into the anterior part of the third ventricle (in goats). The results are surprising. Although the latency to drink is a little longer than is observed with an equivalent infusion of Sodium salts, once commenced the drinking is virtually continuous. Indeed, the drinking was so persistent that the animal had to be physically restrained from drinking in order to prevent serious overhydration. It could be argued that this Potassium-induced drinking, whether as a consequence of intravenous or intracranial infusion, represents an example of 'antidotal drinking' (Smith, Balagura and Lubran, 1970). These authors found that following gastric infusions of Lithium Chloride (a toxic substance used in the treatment of manic-depressive states), rats drank much more water than



they would if given an equal load of the non-toxic but related salt Sodium Chloride. This they attributed to the rat attempting to clear the unpleasant substance by 'flushing out' the system. However, it is felt that whilst this is a valid argument in the case of Lithium, it does not significantly damage the theory presented here. This is because the Lithium Chloride was administered into the gut. The presence of a toxic substance in the stomach could easily be detected by the type of receptor described by Deutsch (1978), and it would surely be a natural response of the rat to attempt to flush this out by drinking excess water. Under natural conditions, the diet of the rat is very varied, and thus to develop such protective responses would be highly advantageous. In addition, 10 ml of Lithium solution was a presumably the rat would be able to detect this, and associate it with the unpleasant effects that followed. However, it is considered unlikely that rats would have evolved similar responses for intracerebral, or even vascular infusions of substances, especially ones that are naturally present, as is Potassium. The doses of Potassium given are generally physiological in size. Thus to argue that the response to Potassium administration is a case of antidotal drinking would be like saying that the normal response to a headache is to down a pint of water.

It is clear from this experiment alone that both the 'Sodium receptor' theory of Andersson and his colleagues, and the somewhat more popular 'cellular dehydration' theory, originated by Gilman (1937) are inadequate. In the next section, further studies of drinking stimulation are

assessed, and methods by which they can be formed into a coherent theory examined.

The model proposed here is shown in Figure 15.1. As one would perhaps expect from the preceding discussion, it incorporates the Na/K pump, as well as means of 'non-specific' active transport of both Sodium and Potassium ions. Although of course the Na/K pump necessitates complementary transfer of ions across the cell membrane, this is not the case with the non-specific transport mechanisms. One factor they do have in common however is that both are active processes, and thus draw upon the reserves of glucose within the cell. It is appreciated that the actual energy substrate is ATP of course, but since the precursor of this ATP is glucose, a simplification was introduced to the model. Except perhaps in the very short term, active ion transport, ATP utilisation and glucose hydrolysis would be very closely related. Consequently, although any self-respecting biochemist would undoubtedly cringe at the prospect, the terms 'glucose', 'ATP', and 'energy substrate' are considered to be virtually interchangeable for current purposes.

The cellular supply of glucose is replenished by facilitated diffusion across the cell membrane from the extracellular spaces. As was discussed earlier, this process does not involve active transport (i.e. it is passive), and thus is directly proportional to the concentration gradient between the extracellular and intracellular spaces. Provided extracellular concentration is held constant, this means

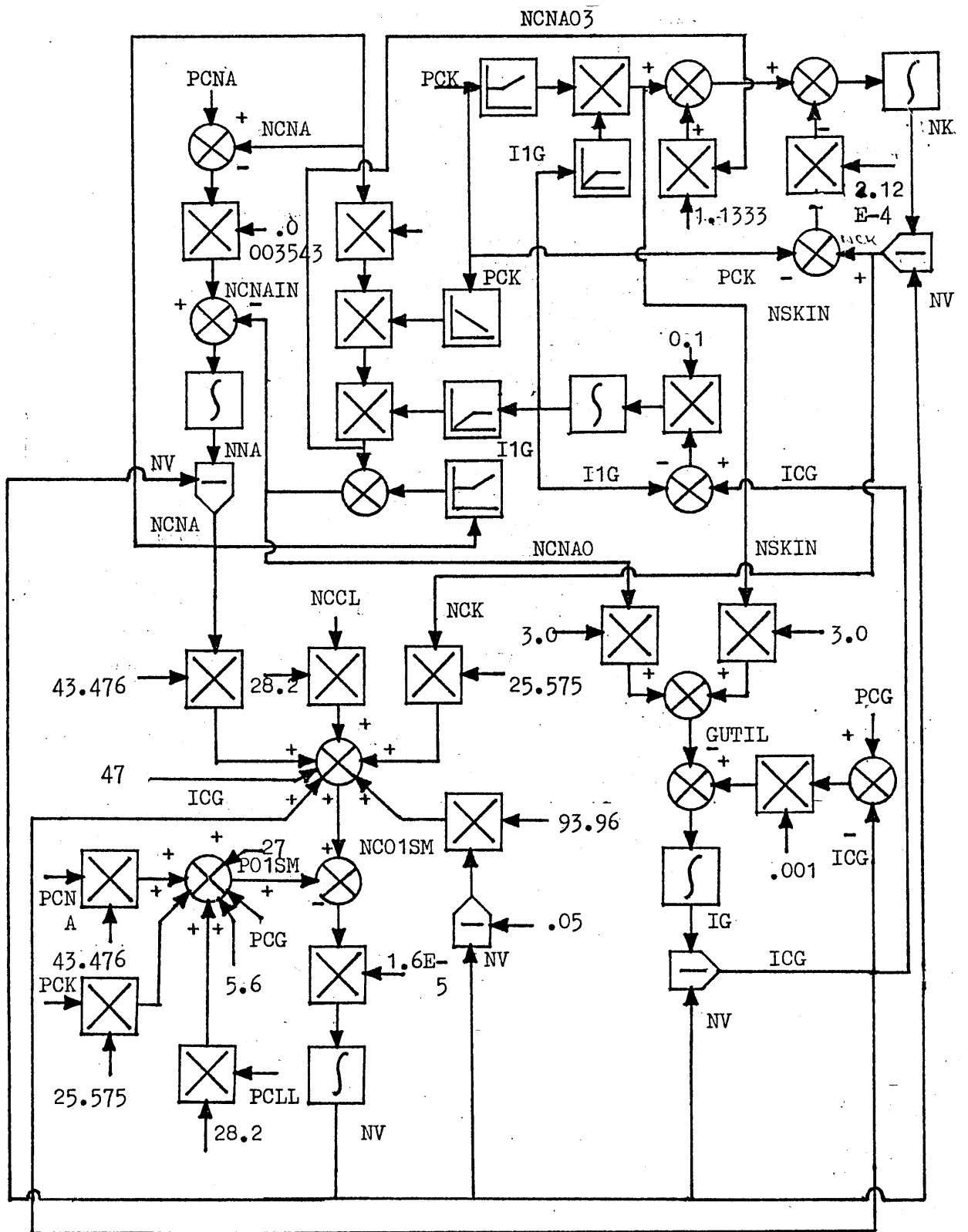


FIGURE 15.1- NEURAL INTRACELLULAR SYSTEM.

that increased ATP (glucose) utilisation due to accelerated ion transfers would result in a more rapid transfer of glucose across the membrane, because the intracellular concentration of glucose would have fallen.

The transfer of ions down a concentration gradient is entirely passive. No energy is required, and the permeability of the cell membrane remains constant. It is in order to counteract these passive flows of Sodium and Potassium that the active transport systems exist.

As has already been discussed elsewhere, there are two limiting factors on rate of active ion transfer. The first is the intracellular concentration of glucose, which may be taken to mean the energy availability. During development of this model, there was some debate as to whether the appropriate rate-limiting factor is total cellular glucose or intracellular glucose concentration. It was decided that the latter is more realistic. The real limiting factor is not glucose per se, but its availability at the sites of ion transport. For example, one can conceive of a grossly overhydrated cell that would have a normal amount of total energy substrate. The concentration of glucose however, and thus the probability that any given transport site will receive an ATP molecule, would be less than normal. The availability of energy substrate can only act as a limiting factor in the determination of active ion transport. Thus an excess of glucose will not accelerate ion transport above the basal level determined by ion availability.

The second limiting factor used in this model is the extracellular Potassium concentration. The evidence for

this is reviewed elsewhere in this Chapter. Briefly however, the studies conducted in both non-neural and neural tissue have shown that an increase in extracellular Potassium induces an active uptake by the cells. In the non-neural cell, such as muscle and adipose tissue, the function of this is probably to maintain a safe extracellular concentration of Potassium; it acts as a means of extra-renal Potassium homeostasis. This appears to be mediated, at least in part, by insulin. Nerve cells also demonstrate an increased uptake of Potassium following an increase in extracellular concentration of that ion. In this case however, the function is somewhat different. The whole-body extracellular concentration of Potassium is normally well protected by the type of homeostatic mechanisms discussed earlier. Neurons do not take part in this homeostasis; indeed, one can argue that the object of the homeostatic mechanisms is to preserve optimum conditions for the nervous system, thus they benefit from the exertions of the cells in the rest of the body. Indeed, it may be argued that the major cause of departure from neural intracellular equilibrium values of Potassium and Sodium concentrations is the transmission of consecutive action potentials. The main function of the neural ion homeostasis mechanisms discussed here may be to permit recovery from this effect. The increases in extracellular Potassium concentration are very local, and thus cannot be referred to the whole-body homeostasis mechanisms. Thus in this case, the neurons increase their uptake of Potassium when stimulated by a raised Potassium concentration in the immediate locality in

order to maintain optimum conditions for activity. Both types of cell, neuronal and non-neuronal also possess 'non-specific' Sodium and Potassium transport mechanisms. These employ, as is discussed elsewhere, different transport mechanisms to that used by the Na/K pump, as is illustrated by the former's insensitivity to the administration of ouabain.

All the active transport mechanisms employed here however share the common characteristic of energy utilisation. Any increase in active transport will result in a proportionally increased requirement for ATP, and thus glucose.

This is central to the theory presented here. It is proposed that the stimulus critical to the initiation of intracellular drinking is the relative depletion of intracellular energy supplies. This may sound somewhat strange, but perhaps the situation may be clarified, and the argument given more force by studying the multiplicity of published stimuli to, and inhibitors of, drinking. Thus in the next section, the predicted responses of the model to a variety of stimuli will be examined. First, the 'traditional' stimuli are assessed. Following this, the contribution of stimuli not normally considered to be within the sphere of intracellular drinking are assessed.

Experimental Treatment	Neural Int. Energy	Drinking Observed Experimentally?
-----	-----	-----
Increase Plasma Na+ by 20%	Down	Yes
Increase Plasma K+ by 30%	Down	Yes
Increase Plasma glucose by 100%	Up	No
Decrease Plasma Glucose by 20% (e.g. insulin)	Down	Yes
Decrease cell perm. to glucose (e.g. comp. binding)	Down	Yes
Increase Plasma Na+ by 20% & Plasma Glucose by 50%	Up	No?
Increase Plasma K+ by 30% & Plasma Glucose by 50%	Up	No?
Inhibit Na/K Pump (Cardiac Glycoside)	Up	No

Table 15.1- Effects of various stimuli on predicted and actual drinking behaviour. An increase in intracellular energy reserves ('up' in column one) predicts that no drinking will occur, whilst a decrease ('down') will predict drinking.

The effect of Sodium Chloride Administration

This perhaps is the classic experiment in the area of intracellular-induced drinking. Gamble, Putnam and McKhann (1929) found that rats drink much more water when Sodium Chloride was added to the diet. Gilman (1937) achieved the same result when hypertonic saline was infused intravenously into the dog, a finding since confirmed on many occasions in a variety of animals. Similarly, many researchers have found drinking to be initiated by intracranial injections of hypertonic saline, an observation first published by Andersson (1953) in the goat. McKinley, Denton and Weisinger (1978) have since demonstrated this in another ruminant, (sheep), whereas Blass and Epstein (1971) achieved the same in the rat. The latter authors also showed that the amount drunk by rats is directly proportional to the concentration of saline injected.

How does the model shown in Figure 15.1 predict this? The rate of passive diffusion of Sodium ions into the intracellular spaces is directly proportional to the concentration gradient across the cell membrane. Thus an increase in extracellular Sodium concentration, however local, will induce a corresponding increase in intracellular Sodium. This would result in the activation of two mechanisms, both of which would increase active transport, and hence energy utilisation. First, the increase in intracellular Sodium will directly induce an increase in transport rate, in an attempt to restore intracellular Sodium concentration to optimum levels (see earlier). This implies the presence of a third factor contributing to



active ion transport, but in fact it is not necessary to incorporate it in this model. The application of hypertonic saline induces, as predicted by the 'osmoreceptor' theory of thirst, a passive flow of cell water out of the cell and into the extracellular spaces. This in turn would result in a transient increase in intracellular Potassium concentration; thus, in view of the determinants of passive ion flow, there would also be an increased loss of cellular Potassium to the extracellular compartment. Extracellular Potassium concentration would also rise, and it is this which induces an increase in Na/K pump activity. Because of the 'coupled' nature of the Na/K pump, the resulting response would be to increase intracellular Potassium, and decrease intracellular Sodium back towards optimum concentrations. All this increased pumping places a strain on intracellular energy reserves, resulting in their subsequent depletion. Certainly, as has been discussed elsewhere in this Chapter, intracellular glycogen is severely depleted following sustained stimulation by the application of hyperosmotic substances. It is hypothesised that less severe depletion of intracellular energy reserves are responsible for eliciting drinking.

#### The effect of direct Potassium administration

As has been shown elsewhere, the direct application of Potassium salts to the anterior part of the third ventricle elicits almost continuous drinking in the goat (Olsson, 1969). Unfortunately for the 'osmoreceptor' theory of thirst, this application results not in cellular

dehydration, but cellular swelling, due to the influx of intracellular water.

However, the theory presented here can easily explain the elicitation of drinking resulting from Potassium application. It is hypothesised that this causes the direct stimulation of the local, neuronal Potassium homeostasis systems. The increase in local Potassium concentration dramatically increases active transport rates of Potassium into the cell (indeed, it is probably this that causes the cellular swelling). Because the Potassium is applied directly to the neurons considered responsible, any 'blunting' of the drinking response caused by extra-neural homeostatic mechanisms, renal or otherwise, is circumvented.

Indeed, with this theory one can differentiate between the experiments reporting positive and negative findings with regard to Potassium administration. It is apparent that nephrectomy reduces this 'blunting', and thus intravenous infusion of Potassium salts into nephrectomised rats does produce drinking, although the response is not as marked as those produced by direct application to the C.N.S.

However, the earliest experiments on Potassium administration were completely negative- no drinking at all was elicited. This, too, can be explained by the theory presented here. First, the animals (dogs) were intact. This would have resulted in rapid renal removal of much of the administered Potassium. In addition, the extra-renal Potassium mechanisms would have been operating, and would have further served to blunt any drinking responses.

In the light of the current hypothesis however, it is

interesting to note that the authors reporting no effect of Potassium salts on water intake had administered the Potassium by including it in the diet. Earlier in this Chapter, overwhelming evidence was presented to indicate that extra-renal Potassium homeostasis was linked with, and probably partially determined by insulin levels. The release of insulin subsequent to (and in anticipation of) the ingestion of food would have enabled a more rapid extra-renal uptake of Potassium than would otherwise have been the case. In addition, food ingestion and its subsequent digestion would have elicited an increase in plasma glucose concentrations. This would have provided a ready source of energy for the increased active transport of Potassium by the muscle and adipose tissues concerned. Perhaps more importantly for the theory presented here however, the increased plasma glucose concentration could ensure that enough energy is also available for any increased neuronal uptake of Potassium. Due to the digestion of food, the glucose concentration gradient across the cell walls would have increased, enabling a more rapid flow of energy into the intracellular spaces just when it was needed most. As a consequence, intracellular energy supplies would not be depleted, despite the increased inorganic ion transport rate, and no drinking would ensue. On the other hand, the additional energy reserves are not available when the Potassium salts are injected intravenously; the result is depletion of neural intracellular energy supplies due to accelerated Potassium transport, (despite 'blunting'), and the consequent elicitation of drinking behaviour. A

prediction of this hypothesis is that some Potassium-induced drinking may be possible in high-Potassium, low energy diets fed to previously food-deprived animals. Similar diets, or high-energy diets fed to replete animals would reduce the magnitude of the Potassium-induced effect.

### Infusion of Saccharides and Drinking

When, with the aid of this theory, one tries to estimate the consequences of intra-venous or intra-cranial infusions of hypertonic sugar solutions, several factors have to be considered.

First, with what ease does the sugar diffuse across the cell membranes? Glucose, as a consequence of its necessity for cellular metabolism, passes through with relative ease, by means of facilitated diffusion (see earlier). Other sugars however, especially disaccharides, are virtually excluded from the cells. Thus whilst the former may produce a transient dehydration until both intracellular and extracellular have reached a new equilibrium, the latter type would produce a much more long-lasting dehydration. This would persist until the renal system had coped with the infused load, or it had been otherwise metabolised.

An additional, related factor that needs to be considered is that of competitive binding. As is discussed elsewhere, glucose is transported across the cell membrane by carrier-mediated diffusion. The specificity of carrier proteins for binding is frequently less than that for actual trans-membrane transport. Thus it is considered quite likely

that some saccharides are capable of binding to the carrier protein normally responsible for glucose transport across the cell membrane, but not being transported across. This binding of saccharides other than glucose to the carrier protein would prevent them from transporting glucose, thereby reducing the cellular permeability to glucose and restricting the intracellular energy supply. The model presented here would predict that competitive binding of glucose-transporting sites by other compounds could result in the initiation of drinking.

Second, does the sugar infused contribute to the energy requirements of the cell? Essentially, this question resolves itself to whether it can be readily utilised by glycolysis and the citric acid cycle. If the sugar concerned is capable of doing this, then it is considered unlikely that much, if any, drinking will ensue as a consequence of its administration, either intra-venous or intra-cranial. The relative permeability of the cell membrane to the sugar concerned may modify this however. In the case of a permeant sugar, infusion of a hypertonic solution will at first induce a loss of intracellular fluid, accompanied by a proportionate amount of Potassium. This increase in extracellular Potassium will elicit an increase activity of the Na/K pump. If the administered sugar has not yet reached the intracellular site where it can contribute to energy reserves (or it has not yet been converted to the chemical state in which it can be utilised), then drinking should result as a consequence of the depletion of intracellular reserves.

Glucose and Drinking

As a consequence of the dispute between the proponents of 'osmo-' and 'Sodium'- receptors, alluded to earlier, many investigators have studied the effects of glucose infusions on drinking. Holmes and Gregerson (1950) found that intravenous infusions of hypertonic glucose into dogs caused transient cellular dehydration, and usually, but not always, more drinking than that produced by equivalent infusions of urea or isomannide. On the other hand, Fitzsimons (1971), studying nephrectomised rats, found that intravenous glucose and methyl glucose caused hardly any drinking, and certainly less than equivalent amounts of urea. Olsson (1972) studied the effects of intra-venous infusions of various hypertonic solutions into the goat, with similar results to that of Fitzsimons (1971).

Comparable results have also been achieved following intra-cranial application of hypertonic glucose. Andersson, Jobin and Olsson (1967) found that infusion of 1.7M glucose into the third ventricle of the goat caused no drinking. McKinley, Blaine and Denton (1974) observed similar consequences following hypertonic glucose infusion in the sheep.

This is as would be predicted by the model presented here. Glucose is the energy substrate utilised by the glycolysis/ citric acid cycle. Consequently, adequate supplies would be available to replenish energy reserves, whether or not the active transport of electrolytes has increased.

One interesting prediction of this theory is that the

induction of drinking by the infusion of (say) hypertonic saline could be modified in its magnitude by the concurrent infusion of hypertonic glucose; for best results, both should be done intracranially. Concurrent infusion of hypertonic glucose would enable a more rapid transfer of energy substrate across the cellular membrane, and thus reduce or even eliminate the depletion in intracellular energy reserves that would normally follow administration of hypertonic saline. Intra-cranial infusion is recommended, because this would circumvent the body's mechanisms for glucose homeostasis. Any significant increase in systemic glucose concentration would elicit an increase in insulin concentration, resulting in the rapid absorption of the excess glucose; consequently it may not then be available for neuronal utilisation in its 'moment of need'. In addition, the increase in insulin concentrations would also modify extra-neuronal Potassium (and hence Sodium) metabolism, with unforeseen consequences.

On the other hand, it would also be predicted that the systemic infusion of insulin would exacerbate intracranial hypertonic saline-induced drinking. This is because the insulin would render the animal hypoglycaemic, and thus deprive the relevant neurones of energy.

Although the results are discussed in a different context to that presented here, there is some evidence to suggest that the infusion of glucose does modify saline-induced drinking. Olsson (1975) found that infusions of isotonic (0.3M) or hypertonic (0.5M) glucose into the lateral cerebral ventricle resulted in halving of the amount

of water drunk by the water- deprived goat. Isotonic (0.15M) Sodium Chloride did not have this effect. The fact that isotonic glucose exerts an observable effect does tend to indicate that it does not operate by means of inducing fluid shifts to or from the intracellular compartment.

### The Effects of Infusing Other Sugars

As was discussed earlier, the specific effects of administering any particular sugar depends upon its cell membrane permeability and the extent of any contribution it can make to the cell's energy requirements. Conversion to the most readily utilisable energy substrate, glucose, is possible for most sugars, but this would be expected to impose a delay between administration and any restoration of neural intracellular energy reserves. The eventual repletion would modify the drinking response, but in the meantime, drinking could well be initiated. This is because the sugar infused would induce an osmotic shift of fluid from the neuronal intracellular compartment. In order to restore osmotic equilibrium, Potassium ions would also flow into the extracellular spaces. The consequent increase in local Potassium concentration causes an increase in Na/K pump activity, tending to deplete intracellular energy stores. The permeability of cell membranes to either Sodium or Potassium is greater than that to the much larger glucose molecule, thus energy depletion can occur for a short period, before available extracellular glucose can restore the intracellular deficit.



Fructose, when infused systemically, has been observed to produce some drinking in the nephrectomised rat (Fitzsimons, 1971). Certainly, the effect was much less even than that induced by equivalent urea infusions, but it was greater than the negligible consequences of glucose. Intra-carotid fructose infusions have been observed to induce drinking in the goat (Eriksson, Fernandez and Olsson, 1971). Intra-cranial (0.7M) infusions into the sheep have also elicited drinking (McKinley, Denton and Weisinger, 1978); interestingly, the water intake was significantly greater than the control infusion, but was also significantly less than that produced by hypertonic (0.35M) saline. This tends to confirm the hypothesis, developed above, that infusion of sugars capable of diffusing only slowly across the cell membrane, yet eventually being convertible to a usable energy substrate, will only exhibit a qualitatively different pattern of drinking stimuli.

Sucrose (table sugar) can, as anyone who has ever tackled a diet will know, be utilised by the body. Thus this disaccharide, consisting of equal proportions of glucose and fructose can be broken down, yielding energy reserves. The glucose obviously needs no conversion; fructose but little more (Guyton, 1976, p.882; Metzler, 1977). However, it cannot be taken up by cells in its natural form. Thus one would expect it to exert an osmotic pressure across the cell membrane, resulting in loss of intracellular fluid and Potassium, and a consequent increase in Na/K pump activity, and thus depletion of neural intracellular reserves. Although any final conversion to glucose will alleviate the

situation, one can surmise that in the meantime drinking will have occurred.

Holmes and Gregerson (1950) injected a 50 per cent sucrose solution into the dog jugular vein and found that drinking, and fluid shifts from the intracellular to extracellular compartments followed. These were similar to those caused by equi-osmolar saline infusions. Interestingly, glucose was found to be intermediate in its effects, as it caused a transient dehydration of the intracellular compartment.\*

With regard to sucrose infusions, Fitzsimons (1971) observed very similar effects in the rat to those previously reported by Holmes and Gregersen (1950) in the dog. Provided the initial increase in plasma osmolality induced by the sucrose injection did not exceed about ten per cent, the nephrectomised animals drank just enough water to dilute their fluids to isotonicity. As would have been predicted by the theory discussed here, the monosaccharides, which are readily converted to energy reserves, and which cross the cellular membrane with comparative ease, are much less effective at inducing drinking. Systemic infusion of sucrose into the iguana has also been observed to induce drinking (Fitzsimons and Kaufman, 1977). Finally, McKinley, Denton

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\* Although glucose is normally the only fuel utilised by the brain to provide its energy requirements, after a period (several days in the human) it does begin to adapt to using ketones as an alternative energy supply. At this point, large quantities of ketone bodies build up in the blood, resulting in the clinical condition of ketosis (Guyton, 1976, p.920). It would be interesting to see whether intracranial infusions of ketone bodies under these conditions could modify drinking responses in the same way as glucose modifies them in the normal, unstarved animal.

and Weisinger (1978) found intra-carotid sucrose infusions into the sheep were particularly good at inducing drinking.

The picture is not quite so clear however when one administers sucrose intra-cranially. Olsson (1969) failed to stimulate the thirst mechanism in the goat by infusing sucrose into the anterior ventral part of the third ventricle. On the other hand, McKinley, Blaine and Denton (1974) found sucrose to be an effective dipsogen when dissolved in artificial cerebro-spinal fluid (CSF), but not when dissolved in water. Paradoxically, McKinley, Denton and Weisinger (1978) found that infusion of 0.7M sucrose (dissolved in artificial CSF) into the lateral cerebral ventricle of the sheep induced drinking, whereas similar infusions of 1.0M sucrose did not. However, Peck and Novin (1971) induced drinking in the rabbit, by infusing 1.15MOSM into the lateral preoptic area. Blass and Epstein (1971), and Blass (1974) obtained similar results in the rat, again by injecting the solution into the anteromedial portion of the lateral peoptic area. Thus some of the negative findings may be consequences of injecting into the wrong area.

#### Sorbitol and Drinking

Sorbitol is a sugar-alcohol that cells are incapable of utilising. It cannot be actively transported across the gut wall, and is thus used commercially as a non-fattening food sweetener. Thus, one would expect sorbitol to be an active dipsogen, whether administered systemically or intra-cranially. The increase in osmotic pressure following administration of a hypertonic solution will induce cellular

dehydration, and thus an increase in local Potassium concentration about the neural intracellular compartment. The increase in Na/K pump (as well as non-specific active pump) activity will deplete intracellular energy reserves, and thus trigger drinking.

Holmes and Gregersen (1950) found sorbitol to be an effective dipsogen in the dog. Fitzsimons (1961) found it to be about as effective as urea, in the nephrectomised rat. However, it was not as effective as sucrose. It had little effect on the behaviour of the iguana (Fitzsimons and Kaufman, 1977), but it is not felt that this could be regarded as a good test of the theory presented here, due to possibility of species differences.

#### Urea and Drinking

The presence (or otherwise) of drinking following the administration of hypertonic urea solutions poses a problem for any theory of intracellular drinking, including this one. The 'osmoreceptor' theory would predict the absence of drinking, except perhaps for that induced by transient effects, as cell walls are easily permeated by the solution. Thus no osmotic pressure gradient is created, and no drinking ensues.

However, nearly all authors, including Gilman (1937) and Bellows (1939) show that some drinking does in fact occur. If urea really does cross the cellular membrane that easily, then even the theory presented here does not explain this. However, as Fitzsimons (1979) pointed out, urea does not readily cross the blood-brain barrier. Thus systemic

infusions of hypertonic urea may result in a dehydration of the whole brain, with consequent increases in Potassium concentration in the immediate locality of the neurons. Considering its unique function in the body, it is perhaps a little unfortunate that urea should have been chosen in some of the earlier studies of drinking. Future work may well illustrate important differences between the techniques employed by the body to handle urea and other substances.

The Effects on Drinking of Infusing Other Substances

In preceding sections of this Chapter, the depletion of intracellular energy reserves has always been brought about by increasing energy utilisation by the Na/K and non-specific active transport systems. However, variations in energy store size can be induced by a range of techniques. A prediction of the theory presented here is that any such intervention should be capable of modifying the drinking responses of experimental animals. One of the particularly exciting aspects of this theory is that not only is it capable of explaining the 'traditional' stimuli to intracellular drinking. It can also begin to unify within one theory the wide range of stimuli that have been experimentally observed, but to date have been largely ignored, or mentioned merely as curiosities.

It has long been known that the Na/K pump can be inactivated by application of a range of chemicals called 'cardiac glycosides'. The most commonly studied is ouabain. Arresting the Na/K pump greatly reduces the energy requirements of the neural cells. Consequently the theory would predict an accumulation of energy reserves, and an inhibition of drinking. After initial developments of the theory, two experiments were discovered that confirm this prediction, both in rats (Bergmann, Chaimovitz, et al, 1967) and sheep (Weisinger, Denton and McKinley, 1977). The inhibition of drinking induced by the implantation of ouabain is extremely effective, and entirely prevents any drinking responses to saline, angiotensin and water deprivation (Weisinger, Denton and McKinley, 1977).

As was discussed earlier, insulin induces an uptake of plasma glucose by extra-neural tissues, but not by neurons. In the liver, this glucose is then converted and stored as glycogen. Thus administration of insulin independent of additional glucose will result in a drop in plasma glucose levels, depriving the central nervous system of essential energy substrates. This can be sufficiently severe to produce coma, and even death. However, the current theory would predict that insulin administration would stimulate drinking. This is because the fall in plasma glucose would reduce the trans-cellular concentration gradient, and thus its rate of uptake by the neurons. The consequent relative depletion of intracellular energy reserves would induce drinking.

Again, such an effect has been observed in the rat, by Novin (1964). Significant increases in drinking were observed in both normal and water-deprived rats. Novin (1964) also demonstrated a good dose-response curve showing a positive relationship between amount of insulin injected and water drunk.

Ouabain exerts its inhibitory influence on drinking by removing the cell's need for such large amounts of energy substrate. This energy substrate is, in the most immediate sense, ATP. Glycerol appears to be equally effective in its inhibition of drinking and ADH release (Olsson, Larsson and Liljekvist, 1976). It also happens to be capable of inhibiting ATPase activity (Olsson, 1976), which is essential for the Na/K pump. Thus since glycerol in effect reduces the energy requirements of the neuronal cells, the

inhibition of drinking is as would have been predicted.

Throughout the description of this model, few attempts have been made to be more specific about the exact nature of the energy reserves so crucial to the whole theory. This is partly a consequence of ignorance on the author's behalf. However, it is also a reflection of the intended 'suggestive' nature of the model, just as in its time was the 'osmoreceptor' theory. In addition, there is no evidence extant to assist one in determining the nature of the energy reserve. It would be interesting to see whether any substances are capable of blocking glycolysis and the citric acid cycle, and study the effect of their application on drinking patterns. This could help 'localise' the nature of the relevant energy reserve(s) so frequently alluded to in this Chapter.

#### The Relation of the Theory to Feeding Control

The model described here was originally developed merely in order to provide the most parsimonious yet unifying theory of intracellular-induced drinking possible. The realisation that drinking could be related to the same type of stimulus as could, arguably, determine feeding was totally unexpected, yet fascinating. At last, one can begin to conceive the formulation of a single theory, at the cellular level, that might unify both areas of research.

Given that the stimulus for both eating and drinking could fundamentally be a matter of energy depletion at the neuronal level, one can argue that both eating and drinking subserve the same aim of energy regulation. Similarly, the



close temporal relationships observed in most animals between feeding and drinking could be explained most parsimoniously in terms of this one fundamental determinant. Thus, for example, Deaux and Kakolewski (1971) showed that infusions of water which reduce plasma osmolality leads to increased feeding.

Obviously, the process by which the two may be linked is entirely speculative, but perhaps the argument could be similar to the following.

When an animal eats, the electrolytes originally present (especially Potassium, which is present in far greater quantities than Sodium in most laboratory diets), coupled with the products of digestion, tend to produce a hyperosmotic extracellular fluid. Glucose is initially available for the increased rate of active electrolyte transport, but both the glucose and Potassium elicit the release of insulin. Thus much of the newly-formed glucose is rapidly removed from the extracellular fluid (along with much of the Potassium; see earlier). However, the very efficiency of the glucose homeostasis mechanism, and the lack of insulin effect on the central nervous system, means that paradoxically their energy supplies become relatively depleted. In addition, it is also probable that the neural cells are more sensitive to variations in extracellular Potassium than the extra-neuronal cells, and their 'personal Potassium homeostasis systems' have a greater gain than those in the body generally. The greater gain would ensure a more rapid depletion of energy reserves in these cells than in the rest of the body. This depletion would induce

drinking, to restore the body fluids to isotonicity.

Conversely, though less convincingly, the ingestion of water could elicit feeding. For example, the dilution of the extracellular fluids following drinking would result in a slightly greater loss of Potassium down the concentration gradient from the intracellular compartment. The increase in 'local' concentration of Potassium around the relevant neural cells could stimulate an increase in active transport, and hence depletion of intracellular energy reserves, leading to feeding. The obvious flaw in this argument of course is that on this principle one could predict drinking following administration of pure water, which is nonsense. In addition, how does the system differentiate between a feeding and drinking stimulus? Perhaps the stimulus to drinking elicited by a hyposmolar stimulus is negated by the decreased volemic stimulus (the extracellular fluid will have increased in volume following water ingestion). At any rate, it can be seen that the increased energy loads placed upon the neural intracellular system as a consequence of either drinking or ingesting food would mean that there would always be an optimum combination of the two, the ingestion of which would minimise energy expenditure on active electrolyte transport.

Obviously, much remains to be done. But it is fervently hoped that the reader will perceive the current theory as being a step in a promising, if not correct, direction. I submit it for your attention, and trust it will suffer close examination.

Chapter 16Conclusions, and Future Developments of the ModelsConclusions

This section is necessarily brief, for it is felt that all relevant points have already been brought out at the appropriate places in the thesis.

The 'small rat' simulation has shown the potential value of even relatively small simulations as tools, both for research and education. Such phenomena as sham drinking, diabetes insipidus and the responses to haemorrhage are realistically represented in a model small enough to run on a modern microcomputer. It is felt that such systems will in future be extensively used in education; the start made by this simulation is certainly encouraging. Perhaps it is something of a disservice to habitually term this simulation the 'small rat'; it is, after all, the most complex simulation of rat body fluid dynamics yet published- bar one.

As is mentioned elsewhere, the 'large rat' simulation should still be regarded as an experimental 'test-bed'. Currently, it incorporates two theories that are as yet unproven experimentally. Despite this (or, one could argue, because of) the presence of these theoretical systems, the model has produced some very interesting results. Several ways in which individual drinking stimuli could interact are discussed, including one completely new method. It is hoped that these and the other simulated results will induce

experimental work in new, more fruitful, areas than the sterile wranglings currently being conducted over osmo- and Sodium- receptors.

The energy-based theory of intracellular thirst appears to have stood up to this test exceptionally well, having never predicted drinking when none actually took place. However, the true test must lie in experimentation, as the nature of the theory's integration with the other homeostatic systems of the body is crucial to its performance. For example, it is very susceptible to variations in Potassium concentration in the immediate locality. If future work fails to show, as is predicted, that the body is able to control extracellular Potassium concentrations in the locality to within very fine tolerances, then the theory may need revising. However, as is stated elsewhere, if the theory presented here does little more than create controversy, it will have served its purpose well. No longer will researchers be confined to one of two out-dated theories, and horizons may broaden once again.

The phenomenon of 'voluntary dehydration' has for years awaited an adequate explanation (e.g. Bolles, 1975, p.164). It must come as something of a relief for those who constantly marvel at the customary accuracy of physiological control systems to find that all that was needed to explain this apparent anomaly was a greater depth of physiological analysis.

Future DevelopmentsThe 'Small Rat'

This model, originally developed as an educational model, is now being very successfully employed at Open University Summer Schools every year (Toates, pers. comm.). Except in response to any request that the model's scope of validity be expanded, much further development is not anticipated. It is, of course, possible however that other educational and research establishments may wish to use it, and the model may be adapted to suit their individual needs. For example, the cardiovascular representation is quite good enough to permit its use as an educational model for medical students, and psychology undergraduates may find it useful in understanding feeding and drinking interactions.

The small size of this simulation (relative to the 'large rat') can be an advantage in areas other than education. To date, ecological simulations have bordered on the simplistic. Given an adequate computer however, one could perhaps begin to investigate the contributions of physiologically recognised feeding and drinking stimuli to behaviour of an individual in the context of its existence within a hierarchically structured social system. For example, the lowly-placed rat would generally have poor access to food and water, preferential access being afforded to individuals with a higher status. Thus does the general nutritional and hydrational state of the lowly-placed rat differ from its superior colleague? If so, do extreme environmental stresses (e.g. temperature) have different

consequences for different animals, and is it possible to induce 'revolutions', when the lowly-placed animals must obtain sustenance, whatever the risk? The ability to simulate groups of animals, each of which has a realistic physiological representation, could cast new light on the eternal problem of the allocation of scarce resources. Perhaps one could even contemplate simulating colonies over a period of months or years, and attempting to predict reproductive success, as a consequence of each individual's success in obtaining the varied limited resources necessary for survival.

The 'Large Rat'

It is felt that except where special circumstances dictate, the strongest arguments for development may be made for the 'large rat' simulation. Although the present author considers this system to be still at an experimental stage, it appears to have considerable potential. Apart from 'fine tuning' the model (an everlasting process), there are several systems that could usefully be added.

The work on drinking responses following various deprivation schedules should be extended and refined, as should studies of the interactions between normal feeding and drinking. In the light of the energy-based drinking theory presented in Chapter 15, and the possible links with feeding control, it may even be possible to investigate anticipatory drinking, i.e. drinking associated with a meal, but in anticipation of food ingestion.

The scope of the model could be considerably widened if one were able to incorporate feeding regulation. Of greatest overall significance is that this would necessitate the incorporation of plasma glucose metabolism, under the influence of insulin. The benefits of including this hormonal system are two-fold. First, as mentioned, it would permit the investigation of feeding regulation in the context of the most advanced simulation of rat body fluid dynamics yet devised. Second, insulin has been implicated in the extra-renal homeostasis of Potassium (Bia and DeFronzo, 1980). This would considerably extend the model's validity. Currently, the model is susceptible to variations in Potassium input. It is logical that insulin be involved in

intracellular uptake of both glucose and Potassium; the former represents the end-product of digestion, whilst the latter is so plentiful in most foods as to necessitate some extra-renal homeostatic mechanism, buffering variations in plasma concentration. This is of particular significance considering that the aldosterone system takes about an hour to induce much change in the renal handling of Potassium (Guyton, 1976; see elsewhere in this thesis for further references). With such systems one would be able to investigate why Potassium incorporated in food does not initiate drinking, but the same electrolyte administered intra-cerebrally is extremely effective. The theory developed here of course (see Chapter 15) is that the extra-renal homeostatic mechanisms, triggered by insulin, are so effective as to prevent any significant increase in plasma Potassium concentration. Intra-cerebral application, on the other hand, by-passes these mechanisms, and thus exposes the true dipsogenic effect of Potassium. Further development of this simulation would enable a theoretical examination of this topic.

It must be conceded that currently, the new theory of intracellular drinking lacks biochemical depth. It would be most valuable if one could extend this depth of explanation, and thus be more specific about the actual stimuli.

One class of hormonal systems not represented in this simulation are the brain systems. Of these, the greatest omission is probably that of the brain renin-angiotensin system. This model would provide an ideal vehicle for analysing any relationships between the vascular and



cerebral renin-angiotensin systems.

An additional theoretical system presented for the first time in the large rat simulation is that of the 'additive/inhibitory' interactions of the various drinking stimuli (see Chapter 7). Whilst simulations already conducted have been encouraging, they are far from conclusive. It would be interesting to further investigate this subject, in an attempt to define any 'experimentum crucis' that enables one to determine between this theoretical system and the 'special case' of the additive system, discussed in Chapter 14.

To date, oro-gastric influences on drinking have been notable for their absence in the large rat simulation. It will be necessary to incorporate these at some time in the future. This is despite the fact that the simulations appears to perform realistically without them. As was pointed out by Rolls and Rolls (1982), the fact that a particular stimulus does not appear to be essential in the maintenance of a particular behaviour does not indicate its redundancy. There is no doubt that the rat does have, and can make good use of, oro-gastric and hepatic receptors, and thus deserve a place in this model. This would again increase the model's scope, by enabling simulation of sham drinking, etc.

A particular advantage of any comprehensive simulation is that it could be of benefit to drug companies, in studying and analysing the metabolism of certain drugs, such as diuretics or anorexics. Whilst to date there has been little commercial interest shown in this simulation, it is

felt that the situation can only be improved by incorporating more sub-systems. In recent years, many drug companies have felt themselves to be under pressure to change their attitudes to animal experiments; computer simulations such as this could provide a viable alternative, permitting greater clarity of thought about the metabolic fate of drugs, and thereby making each experiment more incisive in concept.

When developing a physiological model, it is all too easy to disregard the environmental influences on drinking behaviour. Of these, perhaps the most important is the ease with which the rat can gain access to water. The greater the ease of access, and the fewer the potential behaviours competing for the animal's time, then the greater will be the influence of 'secondary' drinking stimuli, and the less that of primary drinking stimuli.\* As Rolls and Rolls (1982) and Bolles (1975) point out, this 'secondary' drinking may, under normal circumstances, actually predominate over the 'primary' controls; whilst admittedly one has to start somewhere, and with measurable phenomena, it is high time that the physiologists started looking outside, as well as inside the animal.

Thus it is felt that future development should see the simulation incorporating attempts to represent such factors as water availability, the risk of predation, taste, and

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\* By 'primary' is meant drinking in response to a physiologically recognisable depletion of body fluids; a homeostatic response. By 'secondary' one is referring to drinking that is non-homeostatic, and does not seem to restore any perceived deficit (Rolls and Rolls, 1982, p.152).

previous experience (e.g. Weisinger, 1975; Barker, Best and Domjan, 1977). The ways in which other behaviours interact, and impinge upon the motivation to drink is of critical importance in understanding the day-to-day behaviour of the rat. Here, one could perhaps make good use of the type of system described by Ludlow (1982). To simulate the natural environment, where stimuli are rarely constant, one could perhaps use a 'random walk' technique. This would tend to make the model's predictions more probabilistic than is currently the case.

Currently, the model does not have any form of Sodium appetite. Such a system would be of considerable benefit. For example, if the simulation were able to learn from its past experiences, then one could examine the transition from drinking water to saline following caval ligation (Fitzsimons, 1964).

It is felt that the physical nature of the intracellular 'fluid' may well have some bearing on the dynamics of the intracellular response to stresses. Currently, the intracellular fluid is generally considered to be a body of water circumscribed by a semi-permeable membrane; this is far from the case. Thus future developments of the model may include assessment of such factors as 'free' and 'bound' intracellular fluid; the buffering capacity of red blood cells, themselves a portion of the intracellular compartment, may also be included. These may, for example, be an additional factor to consider in extra-renal Potassium homeostasis.

Appendix IVariable Descriptions- Chapter 2 (Small Rat)

- AR- Arterial Resistance, ml/s/mmHg.
- A1- Intermediate variable in determination of AM.
- A2- Intermediate variable in determination of AM.
- A6- Right atrial pressure influence on ADH.
- A7- Plasma osmolality influence on ADH secretion.
- BV- Blood volume, ml.
- CV- Vascular-interstitial trans-capillary fluid flow, ml/s.
- CK- Net flow of K<sup>+</sup> to intracellular compartment, mg/s.
- CM- Autonomic effect on heart (cardiac multiplier).
- CN- Net Na<sup>+</sup> flow to intracellular compartment, mg/s.
- CO- Cardiac output, ml/s.
- CP- Capillary pressure, mmHg.
- D1- Intracellular stimulus to drinking. No units.
- D2- Extracellular stimulus to drinking. No units.
- DI- Mean arterio-venous pressure gradient, mmHg.
- DS- Drinking stimulus. No units.
- EV- Extracellular fluid volume, ml.
- FA- Solid matter in intracellular comp. ('fat'), g.
- FD- Solid intracellular matter change, g/s.
- FI- Rate of food ingestion, g/s.
- FO- Food uptake from gastro-intestinal tract, g/s.
- FS- Gastro-intestinal food contents, g.
- HO- Rate of water uptake from gut, ml/s.
- HS- Gastro-intestinal content of water, ml.
- IC- Interstitial colloid osmotic pressure, mmHg.

IH- Intracellular fluid volume, ml.  
FW- Water flow ass. with int. solid matter, ml/s.  
GF- Glomerular filtration rate, ml/s.  
HI- Rate of water ingestion, ml/s.  
IK- Intracellular Potassium concentration, mg/ml.  
IN- Intracellular Sodium concentration, mg/ml.  
IO- Intracellular osmolality, mOsmoles/l.  
IP- Interstitial fluid pressure, mmHg.  
IT- Iteration interval, s.  
IV- Interstitial fluid volume, ml.  
IW- Insensible water loss, ml/s.  
KI- Potassium intake, mg/s.  
KO- Gastro-intestinal K<sup>+</sup> uptake, mg/s.  
KS- Gastro-intestinal content of Potassium, mg.  
K1- Extracellular Potassium, mg.  
K2- Intracellular Potassium, mg.  
LF- Lymph flow, ml/s.  
MS- Mean systemic pressure, mmHg.  
NI- Sodium intake, mg/s.  
NO- Na<sup>+</sup> uptake from gastro-intestinal tract, mg/s.  
NS- Gastro-intestinal content of Sodium, mg.  
N1- Extracellular Sodium, mg.  
N2- Intracellular Sodium, mg.  
PC- Plasma colloid osmotic pressure, mmHg.  
PH- Phase of day. Day=0,night=1.  
PK- Plasma Potassium concentration, mg/ml.  
PN- Plasma Sodium concentration, mg/ml.  
PO- Plasma osmolality, mOsmoles/l.  
PP- Plasma content of protein, mg.

PR- Total peripheral resistance, ml/s/mmHg.

PV- Plasma volume, ml.

RA- Right atrial pressure, mmHg.

RV- Resistance to venous return, ml/s/mmHg.

R1- Intermediate variable in renin-angiotensin system.

R2- Intermediate variable in renin-angiotensin system.

R3- Intermediate variable in renin-angiotensin system.

TE- Ambient temperature, centigrade.

TH- Drinking threshold. No units.

UK- Urinary output of Potassium, mg/s.

UN- Urinary output of Sodium, mg/s.

UO- Urinary output of water, ml/s.

UR- Urea-induced osmolality increase, mOsmole/l.

VR- Venous resistance, ml/s/mmHg.

WF- Total net intracellular-interstitial H<sub>2</sub>O flow, ml/s.

WI- Total osmotic intracell.-interst. water flow, ml.

WR- Osmotic intra.-interst. water flow, ml/s.

Variable Descriptions- Large RatVariable Descriptions- Chapter 4 (Vascular Compartment)

AM- Autonomic activity, fraction of 1.\*

AMR- Summed angiotensin and autonomic effects on AR. N=1.

ANGII- Plasma angiotensin II concentration, ng/ml.

ANGIIR- Effect of angiotensin II on AR. N=1

AP- Arterial pressure, mmHg.

APMULT- Ability of heart to pump against AP. N=1.

APRAP- Arterio-venous pressure gradient, mmHg.

AR- Arterial resistance, ml/s/mmHg.

BAR- Basal arterial resistance, ml/s/mmHg.

BV- Blood volume, ml.

CO- Cardiac output, ml/s.

CON- Int. var. in determination of right atrial pressure.

CP- Capillary pressure, mmHg.

CWP- Net pressure across capillary wall, mmHg.

DIFF- Pressure gradient for venous return, mmHg.

DIFV- Net fluid flow from interstitial to plasma, ml/s.

DIFVC- Fluid flow rate across capillary wall, ml/s.

DPLI- Rate of plasma protein flow into plasma, mg/s.

DPLO- Rate of plasma protein flow out of plasma, mg/minute.

DPPRF- Rate of plasma protein formation, mg/minute.

DPPRL- Rate of plasma protein destruction, mg/minute.

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\* Where variable values are expressed as a ratio, or as a fraction of 1 (e.g. autonomic activity, AM), no dimensions are given. Note that 'N' is an abbreviation for 'normal'. 'Int. var.' is an abbreviation for 'intermediate variable', of no physiological significance.

DPV- Rate of change of plasma volume, ml/s.

DVASD- Rate of vascularity destruction, unit/s.

DVASF- Rate of vascularity formation, units/s.

DVAST- Net rate of vascularity formation, units/s.

H2O4- Flow of water to or from the stomach, ml/s.

IFP- Interstitial fluid pressure, mmHg.

IFPRC- Interstitial fluid protein concentration, mg/ml.

IFV- Interstitial fluid volume, ml.

IH2O7- Flow of water to or from the intestine, ml/s.

IWL- Insensible water loss, ml/s.

KBAR- Constant for basal arterial resistance, ml/s/mmHg.

MSP- Mean systemic pressure, mmHg.

MSPC- Int. var. in determination of mean systemic pressure.

LF- Lymph flow, ml/s.

NETPPR- Net change in plasma protein, mg/minute.

PCOP- Plasma colloid osmotic pressure, mmHg.

PGART- Pressure gradient in the arteries, mmHg.

PPR- Amount of plasma protein, mg.

PPRC- Plasma protein concentration, mg/ml.

PV- Plasma volume, ml.

PVML- Intermediate variable in determination of PCOP.

RAP- Right atrial pressure, mmHg.

RBCV- Red blood cell volume, ml.

RVR- Resistance to venous return, ml/s/mmHg.

TCOP- Interstitial fluid colloid osmotic pressure, mmHg.

TPR- Total peripheral resistance, ml/s/mmHg.

UO- Urinary output, ml/s.

VR- Venous resistance, ml/s/mmHg.



Variable Descriptions- Chapter 4 (Vascular Ion Metabolism)

CLI5- Flow rate of Sodium from the intestine, mg/s.  
CLS6- Flow rate of Sodium from the stomach, mg/s.  
DIFCL1- Chloride ion flow from the interstitial fluid, mg/s  
DIFK1- Interstitial-vascular Potassium flow, mg/s.  
DIFNA1- Sodium ion flow from the interstitial fluid, mg/s.  
DPCL- Net rate of plasma Chloride ion flow, mg/s.  
DPCL1- Rate of Chloride ion flow from the plasma, mg/s.  
DPK- Plasma Potassium content, mg.  
DPK1- Rate of Potassium ion flow from the plasma, mg/s.  
DPNA- Net rate of plasma Sodium flow, mg/s.  
DPNA1- Rate of Sodium ion flow from the plasma, mg/s.  
KI5- Flow rate of Potassium ions from the stomach, mg/s.  
KS9- Flow rate of Potassium ions from the intestine, mg/s.  
NAI4- Rate of Sodium flow from the intestine, mg/s.  
NAS6- Sodium ion flow from the stomach, mg/s.  
PCCA1- Plasma Calcium concentration, mOsmoles/l.  
PCG- Plasma glucose concentration, mOsmoles/l.  
PCHCO3- Plasma bicarbonate concentration, mOsmoles/l.  
PCL- Plasma Chloride ion content, mg.  
PCCL- Plasma Chloride concentration, mg/ml.  
PCCL1- Plasma Chloride concentration, mOsmoles/l.  
PCK- Plasma Potassium concentration, mg/ml.  
PCK1- Plasma Potassium concentration, mOsmoles/l.  
PCNA- Plasma Sodium concentration, mg/ml.  
PCCNA1- Plasma Sodium concentration, mOsmoles/l.  
PK- Plasma Potassium content, mg.  
PNA- Plasma Sodium content, mg.

POSM- Plasma osmolality, mOsmoles/l.  
POP- Plasma osmotic pressure, mmHg.  
UOCL- Urinary output of Chloride ions, mg/s.  
UOK- Urinary output of Potassium ions, mg/s.  
UONA- Urinary output of Sodium ions, mg/s.

Variable Descriptions- Chapter 5 (Interstitial Compartment)

DIFV- Net fluid flow from interstitial to plasma, ml/s.  
DIFVC- Fluid flow rate across the capillary wall, ml/s.  
DPL- Net vascular-interstitial protein flow, mg/s.  
DPLI- Plasma protein flow across capillary wall, mg/s.  
DPLO- Plasma protein loss via lymph fluid, mg/s.  
GRCOP- Capillary wall colloid o.p. gradient, mmHg.  
ICCV4- Fluid flow to the intracellular compartment, ml/s.  
IFP- Interstitial fluid protein, mg.  
IFPR- Interstitial fluid protein, mg.  
IFPRC- Interstitial fluid protein concentration, mg/nl.  
IFV- Interstitial fluid volume, ml.  
IFVML- Intermediate variable in determination of IFPRC.  
LF- Lymph flow, ml/s.  
PCOP- Plasma colloid osmotic pressure, mmHg.  
TCOP- Tissue colloid (interstitial) osmotic pressure, mmHg.

Variable Descriptions- Chapter 5 (Interstitial Ions)

DICCL- Chloride flow from intracellular compartment, mg/s.  
DICK- Intracellular-Interstitial Potassium flow, mg/s.  
DICNA- Intracellular-interstitial Sodium flow, mg/s.

DIFCL- Net interstitial flow of Chloride ions, mg/s.  
DIFCL1- Interstitial-vascular chloride flow, mg/s.  
DIFK- Net interstitial flow of Potassium, mg/s.  
DIFK1- Interstitial-vascular Potassium flow, mg/s.  
DIFNA- Net interstitial flow of Sodium ions, mg/s.  
DIFNA1- Interstitial-vascular Sodium flow, mg/s.  
DPCL1- Vascular Chloride loss, mg/s.  
DPK1- Vascular Potassium loss, mg/s.  
DPNA1- Vascular Sodium loss, mg/s.  
IFCCL- Interstitial Chloride concentration, mg/ml.  
IFCCL1- Interstitial Chloride concentration, mOsmoles/l.  
IFCK- Interstitial Potassium concentration, mg/ml.  
IFCL- Interstitial Chloride ion content, mg.  
IFCK1- Interstitial Potassium concentration, mOsmoles/l.  
IFCNA- Interstitial Sodium concentration, mg/ml.  
IFCNA1- Interstitial Sodium concentration, mOsmoles/l.  
IFHCO3- Interstitial bicarbonate concentration, mOsmoles/l.  
IFK- Interstitial fluid Potassium content, mg.  
IFNA- Interstitial fluid Sodium content, mg.  
IFOP- Interstitial fluid osmotic pressure, mmHg.  
IFOSM- Interstitial fluid osmolality, mOsmoles/l.  
IFV- Interstitial fluid volume, ml.  
PCCA1- Plasma Calcium concentration, mOsmoles/l.  
PCG- Plasma glucose concentration, mOsmoles/l.  
IFOSM- Interstitial fluid osmolality, mOsmoles/l.  
IFV- Interstitial fluid volume, ml.  
PCCA1- Plasma Calcium concentration, mOsmoles/l.

Variable Descriptions- Chapter 6 (Intracellular)

DICCL1- Interstitial-intracellular Chloride flow, mg/s.  
DICCL2- Intracellular-interstitial Chloride flow, mg/s.  
DICCL- Net Chloride ion flow rate, mg/s.  
DICK1- Interstitial-intracellular Potassium flow, mg/s.  
DICK2- Intracellular-interstitial Potassium flow, mg/s.  
DICK- Net Potassium ion flow, mg/s.  
DICNA- Net Sodium ion flow rate, mg/s.  
DICNA1- Interstitial-intracellular Sodium flow, mg/s.  
DICNA2- Intracellular-interstitial Sodium flow, mg/s.  
EH204- Metabolic water produced by breakdown of food, ml/s.  
EH208- Water flow associated with body energy, ml/s.  
ICCK- Intracellular Potassium concentration, mg/ml.  
ICCL- Intracellular Chloride concentration, mg/ml.  
ICCL1- Intracellular Chloride concentration, mOsmoles/l.  
ICCK- Intracellular Potassium, mg.  
ICCK1- Intracellular Potassium concentration, mOsmoles/l.  
ICCL- Intracellular Chloride, mg.  
ICCNA- Intracellular Sodium ion concentration, mg/ml.  
ICCNA1- Intracellular Sodium ion concentration, mOsmoles/l.  
ICCV- Intracellular fluid volume, ml.  
ICCV1- Int. var. in determination of ICCV4.  
ICCV2- As ICCV1  
ICCV3- As ICCV1  
ICCV4- Osmotic shift of intracellular fluid, ml/s.  
ICCV5- Total energy metabolism-related fluid shifts, ml/s.  
ICGRAD- Intracellular-interstitial o.p. gradient, mmHg.  
ICHCO3- Intracellular bicarbonate, mOsmoles/l.  
ICHPO- Intracellular phosphate concentration, mOsmoles/l.  
ICNA- Intracellular Sodium ion content, mg.

ICOP- Intracellular osmotic pressure, mmHg.  
ICORG- Intracellular organic matter, mOsmoles/l.  
ICOSM1- Total intracellular osmolality, mOsmoles/l.  
ICOSM2- Int. var., det. of intracellular osmotic pressure.  
IFCCL- Interstitial Chloride concentration, mg/ml.  
IFCK- Interstitial fluid Potassium concentration, mg/ml.  
IFCNA- Interstitial fluid Sodium ion concentration, mg/ml.  
IFOP- Interstitial fluid osmotic pressure, mmHg.  
MG- Intracellular Magnesium ion concentration, mOsmoles/l.  
IFCNA- Interstitial fluid Sodium ion concentration, mg/ml.

Variable Descriptions- Chapter 6 (Intracellular Ions)

DNCCCL- Chloride efflux to plasma, mg/s.  
DNCK- Potassium ion efflux to plasma, mg/s.  
DNCL- Net rate of Chloride ion flow, mg/s.  
DNCNA- Sodium ion efflux to plasma, mg/s.  
DNK- Net rate of Potassium ion flow, mg/s.  
DNNA- Net rate of Sodium ion flow, mg/s.  
DPCCL- Chloride influx to neural intracellular comp., mg/s.  
DPCK- Potassium ion influx to neural compartment, mg/s.  
DPCNA- Sodium ion influx to neural compartment, mg/s.  
ICHCO3- Neural bicarbonate concentration, mOsmoles/l.  
ICHPO- Neural phosphate concentration, mOsmoles/l.  
ICORG- Neural 'organic' substances, mOsmoles/l.  
MG- Neural Magnesium ion concentration, mOsmoles/l.  
NCCL- Neural Chloride concentration, mg/ml.  
NCCL1- Neural Chloride concentration, mOsmoles/l.  
NCK- Neural Potassium ion concentration, mg/ml.

NCK1- Neural Potassium ion concentration, mOsmoles/l.  
NCL- Neural Chloride content, mg.  
NCNA- Neural Sodium ion concentration, mg/ml.  
NCNA1- Neural Sodium ion concentration, mOsmoles/l.  
NCOP- Neural osmotic pressure, mmHg.  
NCOSM- Total neural osmolality, mOsmoles/l.  
NCOSM1- Neural-vascular osmolality gradient, mOsmoles/l.  
NK- Neural Potassium ion content, mg.  
NNA- Neural Sodium ion content, mg.  
NV- Neural water content, ml.  
OF- Electrolyte concentration gradient effect on ion flow.  
OF1- Intermediate variable in derivation of OF.  
OF2- As OF1  
OF3- As OF1  
PCCL- Plasma Chloride concentration, mg/ml.  
PCK- Plasma Potassium ion concentration, mg/ml.  
PCNA- Plasma Sodium ion concentration, mg/ml.

Variable Descriptions- Chapter 7 (Drinking Decision System)

ANGII- Plasma angiotensin II, pg/ml.  
ICG- Intracellular glucose, mOsmole/l.  
INANG- Angiotensin drinking stimulus.  
INANG1- Inhibition on other stimuli from INANG.  
INANG2- Angiotensin stimulus after inhibition.  
INIC- Intracellular Stimulus to Drinking.  
INIC1- Inhibition on other stimuli from INIC.  
INIC2- Intracellular stimulus after inhibition.  
INRAP- Right atrial pressure drinking stimulus.

INRAP1- Inhibition on other stimuli from INRAP.

INRAP2- Atrial stimulus after inhibition.

RAP- Right atrial pressure, mmHg.

TOTIN- Total drinking stimulus.

Variable Descriptions- Chapter 3 (Stomach)

CARIN- Carbohydrate intake, g/s.

CAS1- Net carbohydrate gain or loss from stomach, g/s.

CAS2- Stomach carbohydrate content, g.

CAS3- Carbohydrate/stomach content ratio, g/g.

CAS4- Delivery rate of carbohydrate to intestine, g/s.

CH202- Water/stomach content ratio, g/g.

CLIN- Intake of Cl- ions, mg/s.

CLS1- Net intake of Cl- ions, mg/s.

CLS2- Stomach Cl- content, mg.

CLS3- Conc. of Cl- relative to total stomach content, g/g.

CLS4- Delivery rate of Cl- to intestine, mg/s.

CLS6- Osmotic shift of Cl- across stomach wall, mg/s.

CLS21- Stomach Cl- free for solution in stomach water, mg.

CLS31- Conc. of Cl- in stomach water, mg/ml.

CLS32- Conc. of Cl- in stomach water, mOsmoles/l.

FATIN- Intake rate of fat, g/s.

FAS1- Net intake rate of fat, g/s.

FAS2- Stomach fat content, g.

FAS3- Conc. of fat relative to total stomach contents, g/g.

FAS4- Delivery rate of fat to the intestine, g/s.

FH20IN- Water intake as a constituent of food, g/s.

FOSC- Dry matter/stomach content ratio, g/g.

FOSV- Stomach food (dry matter) content, g.  
H2OIN- Water intake due to drinking, g/s.  
H2O1- Net water loss/gain from stomach, g/s.  
H2O2- Stomach water content, g.  
H2O3- Rate of water delivery to the intestine, g/s.  
H2O4- Osmotic shift of water across stomach wall, g/s.  
INDIN- Intake rate of indigestible matter, g/s.  
INDS1- Net intake of indigestible matter, g/s.  
INDS2- Stomach indigestible matter content, g.  
INDS3- Indigestible matter/stomach content ratio, g/g.  
INDS4- Indigestible matter delivery to stomach, g/s.  
KH2O2- Intermediate var. in determining KH2O3.  
KH2O3- Variable to determine stomach emptying rate, g/s.  
KIN- Intake of Potassium ions, mg/s.  
KS1- Net K<sup>+</sup> intake, mg/s.  
KS2- Stomach K<sup>+</sup> content, mg.  
KS3- Conc. of K<sup>+</sup> relative to total stomach contents, g/g.  
KS4- Delivery rate of K<sup>+</sup> to intestine, mg/s.  
KS5- Fluid conc. of K<sup>+</sup>, mOsmoles/l.  
KS6- Osmotic pressure exerted by K<sup>+</sup> in stomach, mmHg.  
KS7- Osmotic pressure exerted by plasma K<sup>+</sup>, mmHg.  
KS8- K<sup>+</sup> o.p. gradient across stomach wall, mmHg.  
KS9- Osmotic shift of K<sup>+</sup> across stomach wall, mg/s.  
KS31- Stomach K<sup>+</sup> free for solution, mg.  
KS32- Stomach K<sup>+</sup> dissolved in stomach fluid, g.  
KS33- Stomach water K<sup>+</sup> concentration, mg/ml.  
NAIN- Sodium ion intake, mg/s.  
NACL1- Plasma concentration of NaCl, mOsmoles/l.  
NAS1- Net change in stomach Na<sup>+</sup> content, mg/s.



NAS2- Stomach Na<sup>+</sup> content, mg.

NAS3- Ratio of stomach Na<sup>+</sup> to stomach content, mg/g.

NAS4- Delivery rate of Na<sup>+</sup> to the intestine, mg/s.

NAS6- Osmotic transfer of Na<sup>+</sup> across stomach wall, mg/s.

NAS21- Na<sup>+</sup> free for solution in stomach water, mg.

NAS31- Na<sup>+</sup> concentration in stomach water, mg/ml.

NAS32- Osmolality of stomach Na<sup>+</sup>, mOsmoles/l.

PCCL1- Plasma conc. of Cl<sup>-</sup> ions, mOsmoles/l.

PCK1- Plasma conc. of K<sup>+</sup> ions, mOsmoles/l.

PCNA1- Plasma conc. of Na<sup>+</sup> ions, mOsmoles/l.

PHASE- Phase of day.

PRIN- Intake of protein, g/s.

PRS1- Net intake rate of protein, g/s.

PRS2- Stomach protein content, g.

PRS3- Protein/stomach content ratio, g/g.

PRS4- Stomach delivery rate of protein to intestine, g/s.

SFM- Stomach filling multiplier.

SFM1- Version of SFM for determining ion osmotic pressures.

SNACL1- Stomach delivery rate of NaCl to intestine, mg/s.

SOSM1- Stomach content osmolality, mOsmole/l.

SOSM3- Osmotic pressure gradient across stomach wall, mmHg.

SOSM4- Stomach NaCl concentration, mOsmoles/l.

SOSM5- Osmotic pressure exerted by Na<sup>+</sup> and Cl<sup>-</sup> ions, mmHg.

SOSM6- O.P. gradient across stomach wall due to NaCl, mmHg.

STOSM- O.P. exerted by stomach inorganic ions, mOsmole/l.

SVIS- Ratio expressing viscosity of stomach contents.

SVOL- Volume of stomach contents, (solid and liquid), g.

VOP1- Total plasma inorganic ion concentration, mOsmole/l.

Variable Descriptions- Chapter 8 (Intestine)

- CAIG- Intestinal uptake of carbohydrate, g/s.
- CAIK- Intermediate variable in determination of CAIG.
- CAI1- Net gain or loss of carbohydrate, g/s.
- CAI2- Digestible carbohydrate delivery, g/s.
- CAI3- Intestinal carbohydrate content, g.
- CAS4- Influx of carbohydrate from the stomach, g/s.
- CLI1- Cl- available for uptake after faecal loss, mg/s.
- CLI2- Net Cl- shift, mg/s.
- CLI3- Total intestine Cl-, mg.
- CLI4- Ratio of Cl- to NaCl- in intestine.
- CLI5- Total shift of Cl-, both passive and active, mg/s.
- CLS4- Influx of Cl- from the stomach, mg/s.
- FAIG- Intestinal uptake of fat, g/s.
- FAIK- Intermediate variable in determination of FAIG.
- FAI1- Net gain or loss of fat, g/s.
- FAI2- Digestible fat delivery rate, g/s.
- FAI3- Intestinal fat content, g.
- FAS4- Influx of fat from the stomach, g/s.
- IH201- Intestinal water delivery, less faecal loss, g/s.
- IH202- Net intestinal flow of fluid, g/s.
- IH203- Intestine fluid content, g.
- IH204- Active NaCl transport-induced water flow, g/s.
- IH205- Passive NaCl transport-induced water flow, g/s.
- IH206- Fluid flow as a consequence of K<sup>+</sup> transport, g/s.
- IH207- Total fluid shift across the intestine wall, g/s.
- INDI1- Net flow of indigestible matter, g/s.
- INDI2- Intestinal indigestible matter content, g.

- INDI3- Faecal loss of indigestible matter, g/s.
- INDS4- Influx of indigestible matter from the stomach, g/s.
- IVOL- Total volume of all intestine contents, g.
- KCA- Constant determining carbohydrate uptake, g/s.
- KFA- Constant determining fat uptake, g/s.
- KI1- Intestinal K<sup>+</sup> delivery less faecal loss, mg/s.
- KI2- Net transfer of K<sup>+</sup>, mg/s.
- KI3- Total intestine K<sup>+</sup>, mg.
- KI4- Conc. of K<sup>+</sup> in intestine water, mg/ml.
- KI5- Osmotic pressure exerted by intestinal K<sup>+</sup>.
- KI6- K<sup>+</sup> o.p. gradient across intestine wall, mmHg.
- KI7- Intermediate variable in determination of KI8.
- KI8- Shift of K<sup>+</sup> across intestine wall, mg/s.
- KPRI- Constant determining fat uptake, g/s.
- KS7- Osmotic pressure exerted by vascular K<sup>+</sup>, mmHg.
- NACLI1- Intestine content of NaCl, mg.
- NACLI2- Conc. of NaCl in intestinal fluid, mg/ml.
- NACLI3- Osmotic pressure exerted by NaCl, mmHg.
- NACLI4- NaCl o.p. gradient across intestine wall, mmHg.
- NACLI5- Intermediate variable in determination of NACLI6.
- NACLI6- Passive shift of NaCl across intestine wall, mg/s.
- NACLI7- Active shift of NaCl across intestine wall, mg/s.
- NACLI8- Total NaCl shift across intestine wall, mg/s.
- NAI1- Sodium available for uptake, after faecal loss, mg/s.
- NAI2- Net Na<sup>+</sup> flow rate, mg/s.
- NAI3- Intestine content of Na<sup>+</sup>, mg.
- NAI4- Uptake of Na<sup>+</sup>, mg/s.
- NAS4- Influx of Na<sup>+</sup> from the stomach, mg/s.
- PRIAA- Intestinal uptake of protein, g/s.

PRIK- Intermediate variable indetermination of PRIAA.  
PRI1- Net gain or loss of protein, g/s.  
PRI2- Digestible protein delivery, g/s.  
PRI3- Intestinal protein content, g.  
PRS4- Influx of protein from the stomach, g/s.

Variable Descriptions- Chapter 8 (Energy Metabolism)

CAE- Energy from carbohydrate digestion, cal/s.  
CAIG- Intestinal uptake of carbohydrate, g/s.  
EH201- Metabolic water from carbohydrate digestion, ml/s.  
EH202- Metabolic water from fat digestion, ml/s.  
EH203- Metabolic water from protein digestion, ml/s.  
EH204- Total metabolic water from digestion, ml/s.  
EH205- Water flow resulting from glycogen shift, ml/s.  
EH206- Water flow ass. with fat energy store shift, ml/s.  
EH207- Water flow ass. with protein energy shift, ml/s.  
EH208- Total water flow due to body energy stores, ml/s.  
EIN- Total energy supply from digested food, cal/s.  
EIN1- Net energy supply/deficit, cal/s.  
EIN2- Net energy flow to protein energy store, cal/s.  
EIN3- Energy transfer to or from fat energy store, cal/s.  
FAE- Energy supply from digested fat, cal/s.  
FAIG- Intestinal uptake of fat, g/s.  
FAT- Body fat, g.  
FAT1- Rate of body fat change, g/s.  
FW- Weight of body fluids, g.  
GLY- Body glycogen, g.  
GLY1- Rate of change of body glycogen, g/s.

H2O2- Stomach water content, g.  
ICCV- Intracellular fluid volume, ml.  
IFV- Interstitial fluid volume, ml.  
IH2O2- Intestine water content, g.  
MR- Metabolic rate, cal/s.  
PHASE- Day or night.  
PR- Body protein, g.  
PRIAA- Intestinal uptake of protein, g/s.  
PRE- Energy supply from digested protein, cal/s.  
PR1- Rate of change of body protein, g/s.  
PV- Plasma volume, ml.  
WEIGHT- Body weight, g.

Variable Descriptions- Chapter 9 (Renal System)

ALD16- Aldosterone effect on electrolyte reabsorption.  
APRAP- Arterio-venous pressure gradient, mmHg.  
CCLR- Cl- reabsorption by collecting duct (single), mg/s.  
CKS- Collecting duct secretion of Potassium (single), mg/s.  
CNAR- Na+ reabsorption by collecting duct (single), mg/s.  
CNARF- Fractional Sodium reabsorption by collecting duct.  
CRF- Fractional water reabsorption by collecting duct.  
CRR- Water reabsorption by collecting duct, nl/s.  
FF- Glomerular filtration fraction.  
GFR- Glomerular filtration rate (total), ml/s.  
HCLL- Cl- flow rate out of loop of Henle (single), mg/s.  
HCLR- Cl- reabsorption by loop of Henle (single), mg/s.  
HEF- Flow of water out of the loop of Henle (single), nl/s.  
HKL- K+ flow rate out of loop of Henle (single), mg/s.

HKR- Potassium reabsorption by loop of Henle, mg/s.  
HNAL- Sodium flow rate out of loop of Henle (single), mg/s.  
HNAR- Sodium reabsorption by loop of Henle (single), mg/s.  
HRR- Water reabsorption by loop of Henle, nl/s.  
KPRR- Fluid proportion reabsorbed by proximal tubule.  
PCCL- Plasma Chloride concentration, mg/ml.  
PCK- Plasma Potassium concentration, mg/ml.  
PCNA- Plasma Sodium concentration, mg/ml.  
PCOP- Plasma colloid osmotic pressure, mmHg.  
PCOPE- Colloid o.p. at efferent end of glomerulus, mmHg.  
PGC- Glomerular capsule pressure, mmHg.  
PPCE- Plasma protein conc., efferent glomerulus, mg/ml.  
PPRC- Plasma protein concentration, mg/ml.  
PPCINC- Proportionate efferent glom. protein conc.  
PRCLL- Chloride flow out of proximal tubule (single), mg/s.  
PRCLR- Cl- reabsorption by proximal tubule (single), mg/s.  
PREF- Proximal efferent water flow (single), nl/s.  
PRKL- Potassium flow out of proximal tubule (single), mg/s.  
PRKR- K+ reabsorption by proximal tubule (single), mg/s.  
PRNAL- Sodium flow out of proximal tubule (single), mg/s.  
PRNAR- Na+ reabsorption by proximal tubule (single), mg/s.  
PRR- Proximal tubular water reabsorption (single), nl/s.  
PT- Renal tubular pressure, mmHg.  
PUF- Mean glomerular ultrafiltration pressure, mmHg.  
PUFA- Afferent glomerular ultrafiltration press., mmHg.  
PUFE- Efferent glomerular ultrafiltration press., mmHg.  
PUF1- Total glomerular ultrafiltration pressure, mmHg.  
PVBV- Ratio of plasma volume to blood volume.  
PVRBCV- Ratio of plasma to red blood cell volume.

RA- Glom. afferent resistance to blood flow, nl/s/mmHg.  
RE- Glom. efferent resistance to blood flow, nl/s/mmHg.  
RT- Total glomerular resistance to blood flow, nl/s/mmHg.  
SNCLFR- Single nephron glomerular filt. of Cl-, mg/s.  
SNCLUO- Single nephron urinary output of Cl-, mg/s.  
SNGBF- Single nephron glomerular blood flow, nl/s.  
SNGFR- Single nephron glomerular filtration rate, nl/s.  
SNGPF- Single nephron glomerular plasma flow, nl/s.  
SNGPFE- Efferent single nephron glom. plasma flow, nl/s.  
SNKFR- Single nephron glom. filtration rate of K+, mg/s.  
SNKUO- Single nephron urinary output of Potassium, mg/s.  
SNNAFR- Single nephron Cl- glom. filtration rate, mg/s.  
SNNAUO- Single nephron urinary output of Sodium, mg/s.  
UO- Urinary output of water (total), ml/s.  
UOCL- Urinary output of Chloride ions, mg/s.  
UOK- Urinary output of Potassium ions, mg/s.  
UONA- Urinary output of Sodium ions, mg/s.

Variable Descriptions- Chapter 9 (Insensible Water Loss)

ADH- Plasma anti-diuretic hormone concentration, ng/l.  
IWL- Insensible water loss, ml/s.  
PIWL- Pulmonary insensible water loss, ml/s.  
SIWL- Salivary insensible water loss, ml/s.  
TEMP- Ambient temperature, degrees centigrade.

Variable Descriptions- Chapter 10 (Renin-Angiotensin)

ADH- Plasma anti-diuretic hormone concentration, ng/ml.

AM- Autonomic activity (normal=1)  
ANGI- Plasma angiotensin I concentration, ng/ml.  
ANGI1- Angiotensin I formation rate, ng/s/ml.  
ANGI2- Angiotensin I formation rate, ng/s.  
ANGI3- Net angiotensin I production rate, ng/s.  
ANGI4- Total angiotensin I, ng.  
ANGII- Plasma angiotensin II concentration, ng/ml.  
ANGII1- Angiotensin II formation rate, ng/s.  
ANGII2- Net angiotensin II formation rate, ng/s.  
ANGII3- Total angiotensin II, ng.  
ANGII4- Destruction rate of angiotensin II, ng/s.  
BV- Blood volume, ml.  
CO- Cardiac output, ml/s.  
CPO- Cardiac output of plasma, ml/s.  
HBF- Hepatic blood flow, ml/s.  
HKL- Flow rate of K<sup>+</sup> from loop of Henle, ng/s.  
HNAL- Flow of Na<sup>+</sup> from loop of Henle, ng/s.  
HPF- Hepatic plasma flow, ml/s.  
HPF1- Hepatic plasma clearance rate of renin, ml/s.  
PGC- Glomerular capillary pressure, mmHg.  
PV- Plasma volume, ml.  
PVBV- Haematocrit (ratio of plasma to blood).  
RAP- Right atrial pressure, mmHg.  
REN- Plasma renin concentration, ng/ml.  
REN1- Net renin production rate, ng/s.  
REN2- Total renin, ng.  
REN5- Renin destruction rate, ng/s.  
RSR- Renin secretion rate, ng/s.  
RSR1- Renin secretion rate due to autonomic activity, ng/s.



RSR2- Renin secretion due to right atrial pressure, ng/s.  
RSR3- Glomerular cap. press. effect on renin, ng/s.  
RSR4- Efferent Henle Na<sup>+</sup> effect on renin, ng/s.  
RSR5- Summed renin secretion rates, ng/s.  
RSR8- Renin secretion after ADH, K<sup>+</sup> and ang.II, ng/s

Variable Descriptions- Chapter 11 (Aldosterone)

ALD- Plasma aldosterone concentration, ng/ml.  
ALD1- Plasma osmolality effect on aldosterone, ng/s.  
ALD2- Angiotensin effect on aldosterone, ng/s.  
ALD6- Total aldosterone secretion rate, ng/s.  
ALD7- Net aldosterone secretion rate, ng/s.  
ALD8- Total aldosterone in extracellular fluid, ng.  
ALD9- Hepatic clearance of aldosterone, ng/s.  
ALD10- Total aldosterone clearance, ng/s.  
ALD11- Renal aldosterone clearance, ng/s.  
ALD15- Intermediate variable in determination of ALD16.  
ALD16- Aldosterone effect on renal reabsorption.  
ALD17- Intermediate variable in determination of ALD16.  
ANGII- Plasma angiotensin II concentration, ng/ml.  
ECFV- Extracellular fluid volume, ml.  
GFR- Glomerular filtration rate, ml/s.  
ICCK- Plasma Potassium concentration, mg/ml.  
ICCNA- Plasma Sodium ion concentration, mg/ml.  
IFV- Interstitial fluid volume, ml.  
PCR- Ratio of plasma Potassium to Sodium.  
PV- Plasma volume, ml.

Variable Descriptions- Chapter 12 (Anti-Diuretic Hormone)

ADH- Plasma anti-diuretic hormone concentration, ng/s.  
ADH1- Right atrial pressure influence on ADH release.  
ADH2- Autonomic influence on ADH release.  
ADH3- Intracellular osmolality influence on ADH release.  
ADH4- Total influence on ADH release.  
ADH7- ADH release, after stim/response latency.  
ADH8- Net ADH secretion rate, ng/s.  
ADH9- Total ADH in circulation, ng.  
ADH10- Destruction rate of ADH, ng/s.  
ADH11- Loss of ADH due to glomerular filtration, ng/s.  
ADH12- Total loss/destruction of ADH, ng/s.  
KADH1- Constant determining ADH destruction.

Variable Descriptions- Chapter 13 (Autonomic System)

There are a very large number of 'intermediate variables' in this system. Thus to list them all would be unnecessarily wasteful of space. As can be seen from an examination of Fig 13.1, the variables tend to be easily categorised, so only the important variables are described here.

In addition it should be noted that most variables in this system are dimensionless, being expressed in relative terms only.

AM- Autonomic activity.  
AMAOR- Aortic baroreceptor effect on AM.  
AMCAR- Carotid baroreceptor effect on AM.

AMCHE- Carotid body chemoreceptor effect on AM.  
AMCNS- C.N.S. ischaemic response effect on AM.  
AMVEN- Atrial stretch receptor effect on AM.  
AP- Arterial pressure, mmHg.  
CBBF- Carotid body blood flow, ml/s.  
CBPG- Carotid body pressure gradient, mmHg.  
CBF- Cerebral blood flow, ml/s.  
CO- Cardiac output, ml/s.  
ISC\*- Prefix for variables in the cerebral anoxia system.  
RAP- Right atrial pressure, mmHg.

Variable Descriptions- Chapter 15 (Neural Compartment)

GUTIL- Rate of glucose utilisation, mOsmole/s.  
ICG- Intracellular glucose concentration, mOsmoles/l.  
IG- Intracellular glucose, mOsmoles.  
I1G- Intermediate in derivation of NCNAO3.  
NCK- Neural Potassium concentration, mg/ml.  
NCNA- Intracellular Sodium concentration, mg/ml.  
NCNAIN- Sodium flow into compartment, mg/s.  
NCNAO- Sodium transport out, mg/s.  
NCNAO1- Intermediate in Na<sup>+</sup> transport out, mg/s.  
NCNAO2- Intermediate in Na<sup>+</sup> transport out, mg/s.  
NCNAO3- Intermediate in Na<sup>+</sup> transport out, mg/s.  
NCNAO4- Intermediate in Na<sup>+</sup> transport out, mg/s.  
NCO1SM- Neural osmolality, mOsmoles/l.  
NK- Neural Potassium content, mg.  
NNA- Neural Sodium content, mg.

NSKIN- Non-specific Potassium transport, mg/s.

NV- Neural volume, ml.

PO1SM- Plasma osmolality, mOSmoles/l.

Program Listing- 'Small Rat'

```

00001 tim=86400
00020 print "At what interval is data sent to file?"
00025 print "e.g. 3600 secs,86400 secs etc."
00030 input cz
00035 print "For how long is run to last (fraction of a
day)?"
00040 input "E.g. 1 day, .5 day etc.";cx
00050 rem control input of data from file
00055 input "Give name of initialisation dataset";n1$
00060 gosub 7010
00070 input "Give name of output file";n2$
00075 if n2$=n1$ then print "Warning" Output file will
delete Init. file."
00076 if n2$=n1$ then 55
00080 open £5,n2$,output
00085 print "Do you wish to send data for plotting (p) or
just write"
00087 print "to file (w)? If plotting, remember to amend
lines 6200 on."
00090 input an$
00091 an$=str$(an$,1,1)
00098 print "time intra inter pv
00100 rem*** kidney
00110 gf=(cp**2/25218)*it
00120 uo=(-.0003943*ad+.00959)*gf
00130 if ad  $\frac{3}{4}$  = 2.5 then uo=(-.02056*ad+.06)*gf
00140 rem na+& k+ urinary output
00150 u1=(1.71146e-4*pn-3.9055e-4)*it % if u1/it  $\frac{3}{4}$  4e-5
then u1=4e-5*it
00155 if pn > 3.015 then u1=(.02499*pn-.07523)*it
00156 rem aldosterone-induced delay
00157 un=un+((u1-un)*.001*it)
00160 u2=(.3483*pk-.05403)*it % if u2 < 0 then u2=0
00165 uk=uk+((u2-uk)*.001*it)
00170 if uo/un > .0832 then uo=un*.0832
00200 rem*** insensible water loss
00210 iw=.000047*it
00220 if te >= 20 then iw=(.0000106*te-.000165)*it
00230 if ph=1 then iw=iw*2
00300 rem*** adh control. note link with drinking
00310 a6=(-1.2*ra+6)
00315 a7=(.417*po-122.33) % if a7 < 0 then a7=0
00320 aa=a6+a7 % if aa > 0 then aa=0
00330 ad=ad+((aa-ad)*.01*it)
00335 rem for di simulation ad=0
00400 rem*** gastro-int. water
00410 ho=hs*((pn+pk)-((ns+ks)/hs))*0.0002*it % if hs < 1e-5
then ho=0
00420 hs=hs+hi-ho % if hs < 1e-5 then hs=1e-5
00500 rem*** gastro-int. food
00510 fo=fs*.0001*it
00520 fs=fs+fi-fo % if fs < 0 then fs=0
00600 rem*** g-i Sodium
00610 no=ns*.0002*it
00620 ns=ns+(fi*0.7344+hi*nc)-no % if ns < 0 then ns=0

```

```

00700 rem*** g-i potassium
00710 ko=ks*.0002*it
00720 ks=ks+(fi*5.44-ko) % if ks < 0 then ks=0
01000 rem*** intracellular t/o of na & k
01010 ck=(pk*.08721-ik*.0025)*it
01020 k2=k2+ck % ik=k2/ih
01030 cn=(pn*.0025-in*.035325)*it
01040 n2=n2+cn % in=n2/ih
01050 rem*** plasma/ if turnover of na& k
01060 ev=pv+iv
01065 n1=n1+(no-un-cn)
01070 pn=n1/ev
01075 k1=k1+(ko-uk-ck)
01080 pk=k1/ev
01100 rem*** intracellular osmolality
01105 rem note ur this is to allow simulation of urea
infusion
01110 io=in*43.478+ik*25.575+(148*fa*3/ih)+ur
01120 rem*** plasma/ if osmolality
01130 po=pn*43.478+pk*25.575+162.6+ur
01200 rem*** cellular fluid balance
01205 rem osmotic press.gradient effect
01210 wr=(io-po)*.0041667*it
01212 rem reduce loss if i.f.depleted
01213 if wr > 0 then wr=wr*ri
01215 rem total o.p. gradient effect
01220 wi=wi+wr
01225 rem intracellular water
01230 ih=fa*3+wi
01235 rem total fluid flow
01240 wf=fw+wr
01300 rem*** interstitial fluid balance
01310 iv=iv+(cf-lf-wf)
01315 rem this restricts flow out of interstitial comp when
depleted
01316 ri=-.058824*(95.54-iv)+1 % if ri < 0 then ri=0
01317 if ri ÷ 1 then ri=1
01320 rem*** int fluid pressure
01330 ip1=.0165*iv-2.02
01340 if iv ÷ 122.4 then ip1=.055*iv-6.732
01350 rem*** lymph flow
01360 lf=.0002*ip1+.001*it*ri
01370 if ip1 ÷ 0 then lf=.001*ip1+.001*it
01400 rem*** plasma colloid o.p
01410 pc=(pp/pv)**1.6*1767
01500 rem*** cardiovascular system
01505 rem*** plasma volume
01507 pv=pv+(ho+lf)-(uo+iw)-cf
01515 rem*** blood volume
01520 bv=pv+rc
01600 rem*** arterial resistance
01610 ar=(5.2*an+am*.895)*60/it
01620 rem*** total perip1heral resistance
01630 pr=ar+vr
01700 rem*** bv/mean systemic pressure
01710 ms=(bv-11)**2/9.28*am
01800 rem*** cardiac output,art. press.
01810 co=di/rv % if co < 0 then co=0

```

```

01820 ap=pr*co+ra % if ap< 0 then ap=0
01900 rem*** cardiac multiplier
01910 cm=am
01920 if ap< 150 then cm=-.00667*ap+2*am*.8
01930 if cm> 2 then cm=2
02000 rem*** right atrial pressure
02010 ra=ra+(((2.2*co/it/cm-1)-ra)*.1)
02100 rem*** pressure gradient
02110 di=ms-ra
02400 rem*** resistance to venous return
02410 rv=(8*vr+ar)/40
02500 rem*** capillary pressure
02510 cp=ap-(co*ar)
02600 rem*** interstitial colloid o.p.
02610 ic=(1.552/iv)**1.6*1767
02700 rem*** starling's capillary equil.
02710 cf=((cp+ic)-(pc+ip1))*0.00167*it
02720 rem this stops excessive if loss
02730 if cf-lf  $\frac{3}{4}$  0 then cf=cf*ri
02800 rem*** autonomic multiplier
02810 rem*** arterial baroreceptors
02820 a1=-.00666*ap+1.8
02830 if ap< 90 then a1=-.04*ap+4.8
02840 rem*** this kills if ap too low
02850 a2=a2-(((1-(co/it))/400)*it)
02852 if c2 <15 then 2855
02855 if a2 >1 then a2=1
02859 rem***delay
02860 am=(am+((a1-am)*.1))*a2
02870 rem*** receptor adaptation
02880 am=am-(((am-1)/50000)*it)
02885 if am >3.5 then am=3.5
02890 if am <.01 then am=.01
02900 rem*** energy balance
02910 fd=(fo*2739-(((0.58+ph*.1)*(fa/47.867))*it))/8000
02920 rem*** water flow ass. with fat
02930 fw=fd*3
02940 rem*** int. fd for total fat
02950 fa=fa+fd
03100 rem*** renin-angiotensin system
03110 rem*** rap and am influence
03120 r1=(-.002667*ra+.01213)+(.0115*am-.0067)
03125 if r1 <0 then r1=0
03130 rem*** na+ & k+ glom filt influence
03140
r2=(-.0557*(gf/it*pn)+.00923)+(-2.571*(gf/it*pk)+.01534)
03145 if r2 <0 then r2=0
03150 rem*** plasma adh influence
03160 r3=-.00295*ad+.01236
03165 if r3 <0 then r3=0
03170 rem*** sum & delay of above
03180 an=an+(((r1+r2+r3)-an)*.005*it)
03500 rem*** drinking system
03510 rem*** cell's active na+ transport
03520 d1=6666*(in*.035325)-39.67
03525 if d1 <0 then d1=0
03530 rem*** right atrial pressure infl.
03540 d2=-5.5*ra+29.25 % if d2< 0 then d2=0

```

```

03541 rem*** oral metering;note food effect
03542 d3=d3+(hi*-.528)-(d3*1.67e-4*it) % d4=d3+1+fi
03545 rem*** gut content inhibition
03546 d5=(hs+fs)**2/50
03550 rem*** summation
03560 if d1> 10.2and d2 <10 then d2=10
03570 dt=d1+d2+d4-d5
03575 rem*** threshold determination
03580 th=22.3 % if hi> 0 then th=20.5
03590 hi=0
03600 if dt> th then hi=.03*it
03615 if c1< 10 then hi=0
03616 rem hi=0 % rem to water- deprive
03621 rem food intake control
03622 if fd/it< -5e-5 or fa<47.18225 then fi=.00833*it
03623 if fa >48 then fi=0
03624 if fs >5 then fi=0
03630 rem***stops drinking in phys int. no. 3
03640 rem fi=0 % hi=0%ni=0%ki=0
03650 rem this totals water drunk,urinary output
03655 ht=ht+hi %
ut=ut+uo%ft=ft+fi%tn=tn+un%h2=h2+ho%tk=tk+uk%iz=iz+iw
03660 rem resets totals at end of day
03672 if c1/86400=int(c1/86400) then ht=0
03674 if c1/86400=int(c1/86400) then ut=0
03676 if c1/86400=int(c1/86400) then ft=0
03678 if c1/86400=int(c1/86400) then tn=0
03680 if c1/86400=int(c1/86400) then h2=0
03682 if c1/86400=int(c1/86400) then tk=0
03684 if c1/86400=int(c1/86400) then iz=0
04000 ph=1 % rem phase control.night (ph=1) is 6pm to 6am
04005 rem tim equals 86400
04010 if c1-(int(c1/tim)*tim)>21600and
c1-(int(c1/tim)*tim)<64800then ph=0
05000 c1=c1+it
05005 cy=cy+it
05010 if cy=cz and an$="w" then gosub 6000
05011 if cy=cz and an$="p" then gosub 6200
05012 if cy=cz then cy=0.0
05015 if c1< 86400*cx then 100
05020 c1=0.0
05030 close £5
05040 c1=0.0
05050 stop
06000 rem variable dump to file
06005 print "Sending data to file ";n2$
06012 print £5,it
06014 print £5,a1
06016 print £5,a2
06018 print £5,a3
06020 print £5,aa
06022 print £5,ad
06024 print £5,am
06026 print £5,an
06028 print £5,ap
06030 print £5,ar
06032 print £5,bv
06034 print £5,c

```



```
06036 print £5,ck
06038 print £5,cn
06040 print £5,co
06042 print £5,cp
06044 print £5,d1
06046 print £5,d2
06048 print £5,d3
06050 print £5,d4
06052 print £5,d5
06054 print £5,di
06056 print £5,ds
06058 print £5,dt
06060 print £5,ev
06062 print £5,fa
06064 print £5,fi
06066 print £5,fs
06068 print £5,ft
06070 print £5,fw
06072 print £5,gf
06074 print £5,h1
06076 print £5,h2
06078 print £5,h3
06080 print £5,hi
06082 print £5,ho
06084 print £5,hs
06086 print £5,ht
06088 print £5,ih
06090 print £5,i1
06092 print £5,ik
06094 print £5,in
06096 print £5,io
06098 print £5,ip1
06100 print £5,iv
06102 print £5,iw
06104 print £5,iz
06106 print £5,k1
06108 print £5,k2
06110 print £5,ki
06112 print £5,ko
06114 print £5,ks
06116 print £5,lf
06118 print £5,ms
06120 print £5,n1
06122 print £5,n2
06124 print £5,ni
06126 print £5,no
06128 print £5,ns
06130 print £5,ph
06132 print £5,pk
06134 print £5,pn
06136 print £5,po
06138 print £5,pp
06140 print £5,pr
06142 print £5,pv
06144 print £5,r1
06146 print £5,r2
06148 print £5,r3
06150 print £5,ra
```

```
06152 print £5,rc
06154 print £5,rv
06156 print £5,sa
06158 print £5,te
06160 print £5,th
06162 print £5,tk
06164 print £5,tn
06166 print £5,uk
06168 print £5,un
06170 print £5,uo
06172 print £5,ur
06174 print £5,ut
06176 print £5,vr
06190 return
06200 rem this is for variables to be plotted
06210 print £5,c1+.0001
06220 print £5,ap+.0001
06300 return
07000 rem initialisation set uptake
07010 open £4,n1$,input
07020 input £4,it,a1,a2,a3,aa,ad,am,an
07030 input £4,ap,ar,bv,c,ck,cn
07040 input £4,co,cp,d1,d2,d3,d4,d5,di,ds
07050 input £4,dt,ev,fa,fi,fs,ft,fw,gf
07060 input £4,h1,h2,h3,hi,ho,hs,ht,ih,i1,ik,in
07070 input£4,io,ip1,iv,iw,iz
07080 input £4,k1,k2,ki,ko,ks,lf
07090 input £4,ms,n1,n2,ni,no,ns
07100 input £4,ph,pk,pn,po,pp,pr,pv
07110 input £4,r1,r2,r3,ra,rc,rv,sa
07120 input £4,te,th,tk,tn,uk,un,uo,ur,ut,vr
07500 close£4
07510 print"initialisation set name is";n1$
07520 return
```

Program Listing- 'Large Rat'

```
      IMPLICIT REAL*4 (A-Z)
C  INITIALISATION
      PT=8.899
      SNGFR=.2464
      PGC=47.43
      PCOP=26.0
      PCOPE=36.8
      HRR=0.05121
      SNGPF=1.258
      RAP=3.442
      C=0.0
      P=0.0
      AP=115.5
      PRR=0.1467
      PV=12.98
      WEIGHT=300.0
      FW=232.5
      RBCV=7.0
      BV=19.98
      ADH9=35.8378
      AM=0.7196
      ADH7=0.0
      ADH11=.00442
      ADH10=.0939
      ADH12=.09834
      ADH=2.761
      NAIN=0.0
      UONA=0.0005397
      PNA=39.1736
      CLIN=0.0
      UOCL=0.0007902
      PCL=58.5528
      KIN=0.0
      UOK=0.001907
      PK=2.13521
      IFNA=241.534
      IFCL=399.2
      IFK=13.465
      PCG=5.6
      H2OIN=.000
      FOODIN=0.0
      CARIN=0.0
      PRIN=0.0
      FATIN=0.0
      INDIN=0.0
      FH2OIN=0.0
      CO=1.46
      AMCNS=0.0
      AMCNS4=0.0
      T=0
      AMCAR=0.1634
      AMAOR=0.114
      AMCHE4=0.1
      AMCNS7=0.0
      AMBAR7=1.0
```

AMBAR6=10.0  
AMCHE8=0.0  
ISC5=1.0  
CBBF=0.017  
PPR=929.5  
DPLO=0.005  
DPLI=0.005  
PPRC=PPR/(PV\*1000.0)  
CP=22.48  
TCOP=2.956  
IFP=-0.6245  
LF=.00088  
IFV=84.63  
IFPR=1552.0  
IFPRC=IFPR/(IFV\*1000.0)  
RVR=4.2  
TPR=76.71  
BAR=60.52  
TCO=0.0  
VAS=0.7173  
KBAR=63.4  
VR=13.04  
TEMP=20.0  
S=0.0  
M=0.0  
H=0.0  
D=1.0  
PHASE=0.0  
ALD8=91.636  
ALD16=1.068  
HNAL=0.7212E-7  
HKL=0.4313E-8  
RSR=0.004352  
REN2=2.0  
REN5=0.004352  
GFR=0.01519  
ANGII1=0.01234  
ANGI4=0.15  
ANGII4=0.01234  
ANGII3=0.3088  
PVBV=0.634  
APRAP=AP-RAP  
H2O3=0.000183  
H2O4=-0.0003526  
H2O2=2.478  
KH2O3=0.0004297  
NAS4=0.0007914  
NAS32=188.428  
NAS2=10.739  
CLS4=0.002108  
CLS32=325.634  
CLS2=28.60542  
KS4=0.002145  
KS6=1558.0  
KS2=29.1075  
PCK1=4.206  
SFM1=0.0  
IH2O3=1.019

NAI4=0.001956  
NAI3=2.252  
CLI5=0.0  
CLI3=5.998  
KI8=0.000225  
KI3=0.2636  
SNACL1=0.0  
KS9=0.0  
NA3=0.0  
CL3=0.0  
K5=0.0  
CWP=0.06298  
PCNA=PNA/PV  
PCCL=PCL/PV  
PCK=PK/PV  
PCNA1=PCNA\*43.4783  
PCCL1=PCCL\*28.2087  
PCK1=PCK\*25.57545  
NACL1=PCNA1+PCCL1  
ANGII=ANGII3/PV  
ALD10=0.1  
MSP=9.57  
CM=0.8  
DVASD=0.0003  
NAS6=0.0  
CLS6=0.0  
DIFNA1=0.0  
DPNA1=0.0  
DIFCL1=0.0  
DPCL1=0.0  
DIFK1=0.0  
DPK1=0.0  
PCCA1=4.6  
PCHCO3=27.0  
POSM=299.9  
ICCK=713.4  
ICCV=129.6  
TICCV4=0.0  
ICCL=23.885  
ICNA=26.0885  
ICORG=93.96  
MG=30.0  
ICHCO3=10.0  
ICHPO=11.0  
ICCNA=ICNA/ICCV  
IFOP=5380.0  
ICCV4=0.00049  
CAS2=1.721  
CAS4=0.000127  
PRS2=0.7535  
PRS4=0.00005  
FAS2=0.1793  
INDS4=0.0  
INDS2=0.6307  
SVOL=5.831  
FAS4=0.00001  
DICNA=0.0  
DICCL=0.0

DICK=0.0  
ICCCL=ICCL/ICCV  
ICCK=ICCK/ICCV  
MC=0.0  
CAIG=0.0  
CAI3=2.38  
IVOL=7.756  
FAI=0.0  
FAI3=0.5912  
PRIAA=0.0  
PRI3=2.198  
INDI2=2.198  
CIH2O=1.0  
CLI1=0.0  
NAI1=0.0  
NACLI5=-0.2078  
RSR4=0.0  
GLY=0.34  
PR=37.0343  
FAT=6.671  
NK=0.270056  
NV=0.05  
NNA=0.000742  
NCCL=0.1649  
LIMIT=4.0  
IFHCO3=28.3  
AMVEN=0.345  
UOC=3598.0  
HUO=0.0  
HUONA=0.0  
HUOK=0.0  
HUOCL=0.0  
CLS3=28.605/5.831  
CH2O2=2.478/5.831  
CH2O21=1.5  
CLS21=28.605\*1.5  
CLS31=42.9  
NAI2=0.0  
CLI2=0.0  
NACLI1=8.25  
NACLI2=8.2  
NACLI3=5134.8  
VOP3=4950.0  
NACLI4=185.0  
NACLI5=1.85  
NACLI6=0.003013  
NACLI7=0.00761  
NACLI8=0.0106  
CLI4=0.72703  
CLI5=0.0077  
NAI4=0.0029  
FAIG=0.0  
CAE=0.0  
FAE=0.0  
PRE=0.0  
EIN=0.0  
MR=0.6667  
EIN1=-0.6667

```
GLY1=0.0
EIN3=0.0
FAT1=0.0
EH2O7=0.0
EIN2=0.0
INDS3=0.12
INDI1=-0.00051
INDI3=0.00051
ICG=1.60507
I1G=1.60507
NCNA=.19971573
NCK=5.5361463
NCNAO=9.9863E-4
NSKIN=0.0
NCO1SM=300.0
PO1SM=300.0
GUTIL=0.0
NCNAIN=0.0
NCNAO1=0.0
NCNAO2=0.0
NCNAO3=0.0
NCNAO4=0.0
IG=0.078295
KS1=0.0
KS3=5.0
KS31=5.822
KS32=8.733
KS33=2.35
KS5=80.7
DPCK=0.0
INIC=5.0
COUNT=0.0
C MAIN PROGRAM
C KIDNEY
C GLOMERULAR FILTRATION
C AFFERENT ULTRAFILTRATION PRESSURE,mmHg
100 PUFA=PGC-PT-PCOP
C EFFERENT ULTRAFILTRATION PRESSURE,mmHg
PUFE=PGC-PT-PCOPE
C MEAN ULTRAFILTRATION PRESSURE,mmHg
PUF1=PUFA+PUFE
PUF=PUF1/2.0
IF (PUFA-PUFE.LE.0.1E-10) PUF=0.1E-10
C SINGLE NEPHRON GLOMERULAR FILTRATION RATE,nl/s
SNGFR1=PUF*0.0347
SNGFR2=(SNGFR-SNGFR1)/5.0
IF(SNGFR2.LE.0.0) GO TO 180
IF(SNGFR2.GE.0.1E-70) GO TO 190
180 IF(SNGFR2.LE.-0.1E-70) GO TO 190
SNGFR2=0.0
190 SNGFR=SNGFR-SNGFR2
IF (SNGFR.LE.0.1E-10) SNGFR=0.1E-10
C AFFERENT AND EFFERENT RESISTANCES
RA=33.205
RE=24.383
RT=RA+RE
C SINGLE NEPHRON GLOMERULAR BLOOD, PLASMA FLOW,nl/s
SNGBF=APRAP/RT
```

```
C GLOMERULAR PRESSURE, mmHg
  PGC=SNGBF*RE
  PVBV=PV/BV
  SNGPF=SNGBF*PVBV
  IF(SNGPF.LE.0.0) SNGPF=0.00001
C EFFERENT GLOMERULAR PLASMA FLOW, nl/s
  SNGPFE=SNGPF-SNGFR
C EFFERENT PLASMA PROTEIN CONCENTRATION
  PPCINC=SNGPF/SNGPFE
  IF(PPCINC.LE.0.0) PPCINC=0.001
  PPCE=PPCINC*PPRC
C EFFERENT PLASMA PROTEIN COLLOID OSMOTIC PRESSURE, mmHg
  PCOPE=PPCE**1.6*1767.03
C TUBULAR PRESSURE, mmHg
  PT=10.902*SNGFR+6.212
  IF(PT.LE.1.0) PT=1.0
C FILTRATION FRACTION
  FF=SNGFR/SNGPF
C SINGLE NEPHRON FILT. RATE OF Na+, Cl-, K+, mg/s
  SNNAFR=PCNA*(SNGFR*1.0E-6)
  SNCLFR=PCCL*(SNGFR*1.0E-6)
  SNKFR=PCK*(SNGFR*1.0E-6)
C GLOMERULAR FILTRATION RATE, ml/s
  GFR=SNGFR*64000.0/1000000.0
C PROXIMAL TUBULE SYSTEM
C REABSORPTION CONSTANT
  PVRBCV=PV/RBCV
  KPRR=0.8
  IF(PVRBCV.GE.1.57) KPRR=-0.691*PVRBCV+1.884
  IF(KPRR.LE.0.0) KPRR=0.0
C SN Na+ REABSORPTION, LOSS
  PRNAR=SNNAFR*KPRR
  PRNAL=SNNAFR-PRNAR
C SN Cl- REABSORPTION, LOSS
  PRCLR=PRNAR*1.46411
  PRCLL=SNCLFR-PRCLR
C SN K+ REABSORPTION, LOSS
  PRKR=SNKFR*KPRR
  PRKL=SNKFR-PRKR
C SN H2O REABSORPTION, LOSS
  PRR=SNGFR*KPRR
  PREF=SNGFR-PRR
C LOOP OF HENLE SYSTEM
C H2O REABSORPTION, nl/s
  HRR=PREF*0.4036
  IF(PREF.GE.0.05451) HRR=0.809717*PREF-0.022138
  IF(PREF.GE.0.22) HRR=0.23312*PREF-0.104713
C HENLE EFFERENT FLOW, nl/s
  HEF=PREF-HRR
C SODIUM REABSORPTION, mg/s
  HNAR=0.925*PRNAL
  IF(PRNAL.GE.0.46406E-9)
HNAR=0.74343*PRNAL+0.84242E-10
C HENLE Na+ LOSS (EFFERENT FLOW)
  HNAL=PRNAL-HNAR
C CHLORIDE REABSORPTION, MG/S
  PRNAF=HNAR/PRNAL
  HCLR=HNAR*1.46411
```



```
C HENLE Cl- LOSS(EFFERENT FLOW)
      HCLL=PRCLL-HCLR
C POTASSIUM REABSORPTION,mg/s
      HKR=0.92496*PRKL
      IF(PRKL.GE.0.2292E-10) HKR=0.74347*PRKL+0.41596E-11
C HENLE K+ LOSS (EFFERENT FLOW)
      HKL=PRKL-HKR
C COLLECTING DUCT REABSORPTION RATE
      CRF=ADH*0.6233
      IF(ADH.GE.1.5) CRF=0.021198*ADH+0.9032
      IF(ADH.GE.3.2) CRF=0.0014881*ADH+0.96624
      IF(ADH.GE.20.0)CRF=0.996
      CRF=CRF-0.055
      CRR=HEF*CRF
C SINGLE NEPHRON URINARY OUTPUT,nl/s
      SNUO=HEF-CRR
C URINARY OUTPUT,ml/s
      UO=SNUO*0.06403
      IF(UO.LE.0.0) UO=0.0
C COLLECTING DUCT Na+ REABSORPTION RATE,mg/s
      CNARF=ALD16*2.36286
      IF(ALD16.GE.0.35) CNARF=0.13304*ALD16+0.780435
      IF (CNARF.GE.0.995) CNARF=0.995
C THIS DETERMINES POTASSIUM SECRETION
C IT LINKS K+ SECRETION TO NA+ AVAILABILITY.
      CKS=(HNAL*CNARF)*0.02
      IF (PCK.GE.0.16) CKS=CKS+((PCK-0.16)*4.0E-7)
C THIS PARTIALLY 'DE-LINKS' NA+ OUTPUT FROM ALDOSTERONE,
PROVIDING A
C NON-SPECIFIC CHANNEL.
      IF(CNARF.GE.0.995) CNARF=0.995
      CNAR=HNAL*CNARF
      IF(PCNA.GT.3.40001)CNAR=CNAR-((PCNA-3.4)*.664E-7)
C SINGLE NEPHRON Na+ URINARY OUTPUT,mg/s
      SNNAUO=HNAL-CNAR
C SN Na+ UO,NG/S TO UONA, MG/S
      UONA=SNNAUO*64000.0
      IF(UONA.LE.0.0) UONA=0.0
C COLLECTING DUCT Cl- REABSORPTION RATE,mg/s
      CCLR=CNAR*1.46411
C SINGLE NEPHRON Cl- REABSORPTION RATE,mg/s
      SNCLUO=HCLL-CCLR
C SN Cl- UO,NG/S TO UOCL,MG/S
      UOCL=SNCLUO*64000.0
      IF(UOCL.LE.0.0) UOCL=0.0
C SINGLE NEPHRON K+ URINARY OUTPUT
      SNKUO=HKL+CKS
C SN K+ UO,NG/S TO UOK,MG/S
      UOK=SNKUO*64000.0
      IF(UOK.LE.0.0) UOK=0.0
C THIS SYSTEM CALCULATES HOURLY URINARY OUTPUT,AND
FOOD,WATER INPUT
      UOC=UOC+1.0
      IF(UOC.LT.3600.0) GO TO 600
      UOC=0.0
      HUO=0.0
      HUONA=0.0
      HUOK=0.0
```

```

        HUOCL=0.0
        HH2OIN=0.0
        HFIN=0.0
        HIWL=0.0
        HSTOM=0.0
        HINT=0.0
        HKS9=0.0
        HKI8=0.0
        TFWAT=0.0
600    HUO=HUO+UO
        HUONA=HUONA+UONA
        HUOCL=HUOCL+UOCL
        HUOK=HUOK+UOK
        HH2OIN=HH2OIN+H2OIN
        HFIN=HFIN+FOODIN
        HIWL=HIWL+IWL
        HSTOM=HSTOM+H2O4
        HINT=HINT+IH2O7
        HKS9=HKS9+KS9
        HKI8=HKI8+KI8
        TFWAT=TFWAT+FWAT
C INSENSIBLE WATER LOSS,ml/s
C SKIN IWL
        SIWL=0.01*TEMP+0.1
        IF(TEMP.GT.32.6) SIWL=0.7021*TEMP-22.487
        IF(TEMP.GT.38.3) SIWL=2.747*TEMP-102.8
        SIWL=SIWL/12000.0
        IF(PHASE.EQ.1.0) SIWL=SIWL*0.333
C PULMONARY IWL
        PIWL=0.0167*TEMP+0.367
        IF(TEMP.GT.27.1) PIWL=0.222*TEMP-5.222
        IF(TEMP.GT.33.35) PIWL=0.3988*TEMP-11.086
        IF(TEMP.GT.39.6) PIWL=TEMP-35.0
        PIWL=PIWL/12000.0
        IF(PHASE.EQ.1.0) PIWL=PIWL*0.667
C ADH INFLUENCE ON PULMONARY IWL
        PIWLM=1.0
        IF(ADH.GT.3.0) PIWLM=-0.04767*ADH+1.143
        IF(ADH.GT.15.0) PIWLM=0.428
        PIWL=PIWL*PIWLM
C METABOLIC EFFECT ON PIWL (I.E. BINTZ ETC. WORK)
        PIWL=PIWL+ ABS(FAT1*2.41)
        PIWL=PIWL+ ABS(PR1*1.7)
C TOTAL INSENSIBLE WATER LOSS,ml/s
        IWL=SIWL+PIWL
C ADH CONTROL SYSTEM,pg/ml
C RAP/ADH
        ADH1=(-1.206*RAP)+1.261
        IF(RAP.GE.1.0) ADH1=(-0.01381*RAP)+0.06907
        IF(RAP.GE.6.0) ADH1=-0.01379
        IF (ADH1.LE.0.1E-10) ADH1=0.1E-10
C AM/ADH
        ADH2=0.0
        IF(AM.GE.0.6) ADH2=0.18418*AM-0.1289
        IF(AM.GE.1.0) ADH2=8.03915*AM-7.9839
C INTRACELLULAR OSMOLALITY/ADH
        ADH3=0.0
        IF(POSM.GE.294.0) ADH3=0.0199473*POSM-5.90899

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      IF(POSM.GE.299.0) ADH3=0.112698*POSM-33.6417
      ADH4=ADH1+ADH2+ADH3
      IF(ADH4.LE.0.0) ADH4=0.0
C ADH S/R LATENCY
      ADH5=ADH4-ADH7
      IF(ADH5.LE.0.0) GO TO 30
      IF(ADH5.GE.0.1E-70) GO TO 40
30      IF(ADH5.LE.-0.1E-70) GO TO 40
      ADH5=0.0
40      ADH6=ADH5/2.0
      ADH7=ADH7+ADH6
C NET ADH SECRETION, pg/s
      ADH8=ADH7-ADH12
      ADH9=ADH9+ADH8
C PLASMA ADH CONC.
      ADH=ADH9/PV
      KADH2=1.0
      IF(ADH.GE.4.44) KADH2=0.588
      IF(ADH.GE.17.76) KADH2=0.442
      KADH1=KADH2*300.0
C ADH DESTRUCTION
      ADH10=ADH9/KADH1
C RENAL ADH LOSS
      ADH11=ADH*GFR
C TOTAL ADH LOSS
      ADH12=ADH10+ADH11
C STOMACH SYSTEM
C NET H2O STOMACH TURNOVER
      H2O1=H2OIN+FH2OIN-H2O3-H2O4
      H2O2=H2O2+H2O1
      IF(H2O2.LE.0.001) H2O2=0.001
      CH2O2=H2O2/SVOL
      CH2O21=CH2O2*3.333
      IF(CH2O21.GE.1.0) CH2O21=1.0
      H2O3=CH2O2*KH2O3*2.0
      IF(H2O2.LE.0.1E-2) H2O3=0.0
C THIS SYSTEM HOPEFULLY PREVENTS HIGH DELIVERY RATES WITH
LOW H2O2
      IF(H2O2.GE.0.1) GO TO 105
      IF(H2OIN.EQ.0.0) GO TO 105
      IF(H2O3.GT.H2OIN*0.7) H2O3=H2OIN*0.7
C NET NA+ STOMACH TURNOVER
105      NAS1=NAIN-NAS4-NAS6
      NAS2=NAS2+NAS1
      IF(NAS2.LE.0.0025) NAS2=0.0025
      NAS3=NAS2/SVOL
      NAS4=NAS3*KH2O3
      IF(NAS2.LE.0.00305) NAS4=0.0
      NAS21=NAS2*CH2O21
      NAS31=NAS21/H2O2
      NAS32=NAS31*43.47826
C NET CL- STOMACH TURNOVER
      CLS1=CLIN-CLS4-CLS6
      CLS2=CLS2+CLS1
      IF(CLS2.LE.0.002) CLS2=0.002
      CLS3=CLS2/SVOL
      CLS4=CLS3*KH2O3
      IF(CLS2.LE.0.0045) NAS4=0.0

```

```
CLS21=CLS2*CH2O21
CLS31=CLS21/H2O2
CLS32=CLS31*28.2087
C NET K+ STOMACH TURNOVER
KS1=KIN-KS4-KS9
KS2=KS2+KS1
IF(KS2.LE.0.00015) KS2=0.00015
KS3=KS2/SVOL
KS4=KS3*KH2O3
IF(KS2.LE.0.000182) KS4=0.0
KS31=KS2*0.2
KS32=KS31*CH2O21
KS33=KS32/H2O2
KS5=KS33*34.3643
KS6=KS5*19.3
KS7=PCK1*19.3
KS8=KS7-KS6
IF(KS8.LE.0.0) GO TO 610
IF(KS8.GE.0.1E-30) GO TO 620
610 IF(KS8.LE.-0.1E-30) GO TO 620
KS8=0.0
620 KS91=KS8*SFM1
KS92=KS91-KS9
KS93=KS92*0.01
IF(KS93.LE.0.0) GO TO 630
IF(KS93.GE.0.1E-30) GO TO 640
630 IF(KS93.LE.-0.1E-30) GO TO 640
KS93=0.0
640 KS9=KS9+KS93
C STOMACH OSMOLARITY,O.P.
SOSM1=NAS32+CLS32+KS5
STOSM=SOSM1*19.3
C VASCULAR OSMOLARITY,O.P.
VOP1=PCNA1+PCCL1+PCK1
VOP2=VOP1*19.3
C VASCULAR/STOMACH O.P. GRADIENT
SOSM3=VOP2-STOSM
IF(SOSM3.LE.0.0) GO TO 650
IF(SOSM3.GE.0.1E-30) GO TO 660
650 IF(SOSM3.LE.-0.1E-30) GO TO 660
SOSM3=0.0
C STOMACH H2O ABSORPTION
660 H2O41=SOSM3*SFM1
H2O42=H2O41-H2O4
IF(H2O42.LE.0.0) GO TO 220
IF(H2O42.GE.0.1E-70) GO TO 230
220 IF(H2O42.LE.-0.1E-70) GO TO 230
H2O42=0.0
230 H2O43=H2O42*0.01
H2O4=H2O4+H2O43
IF(H2O2.LE.0.1E-2) H2O4=0.0
C STOMACH NACL OSMOLARITY
SOSM4=NAS32+CLS32
SOSM5=SOSM4*19.3
C VASCULAR NACL OSMOLARITY
VOP3=NACL1*19.3
C STOMACH/ VASCULAR NACL GRADIENT
SOSM6=VOP3-SOSM5
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        IF(SOSM6.LE.0.0) GO TO 670
        IF(SOSM6.GE.0.1E-30) GO TO 680
670      IF(SOSM6.LE.-0.1E-30) GO TO 680
        SOSM6=0.0
C STOMACH NACL ABSORPTION
680      SNAC11=SOSM6*SFM1
        SNAC12=SNAC11-SNACL1
        IF(SNAC12.LE.0.0) GO TO 240
        IF(SNAC12.GE.0.1E-70) GO TO 250
240      IF(SNAC12.LE.-0.1E-70) GO TO 250
        SNAC12=0.0
250      SNAC13=SNAC12*0.01
        SNACL1=SNACL1+SNAC13
        NAS6=SNACL1*(NAS2/(NAS2+CLS2))
        CLS6=SNACL1-NAS6
C CARBOHYDRATE STOMACH T/O
        CAS1=CARIN-CAS4
        CAS2=CAS2+CAS1
        IF(CAS2.LE.0.1E-30) CAS2=0.0
        CAS3=CAS2/SVOL
        CAS4=CAS3*KH2O3
C PROTEIN STOMACH T/O
        PRS1=PRIN-PRS4
        PRS2=PRS2+PRS1
        IF(PRS2.LE.0.1E-30) PRS2=0.0
        PRS3=PRS2/SVOL
        PRS4=PRS3*KH2O3
C FAT STOMACH T/O
        FAS1=FATIN-FAS4
        FAS2=FAS2+FAS1
        IF(FAS2.LE.0.1E-30) FAS2=0.0
        FAS3=FAS2/SVOL
        FAS4=FAS3*KH2O3
C INDIGESTIBLE STOMACH T/O
        INDS1=INDIN-INDS4
        INDS2=INDS2+INDS1
        IF(INDS2.LE.0.1E-30) INDS2=0.0
        INDS3=INDS2/SVOL
        INDS4=INDS3*KH2O3
C STOMACH FOOD VOL.
        FOSV=CAS2+PRS2+FAS2+INDS2+((NAS2+CLS2+KS2)/1000.0)
C TOTAL STOMACH VOLUME
        SVOL=H2O2+FOSV
        IF(SVOL.LE.0.1E-30) SVOL=0.0
C STOMACH FOOD/VOLUME RATIO
        FOSC=FOSV/SVOL
C VISCOSITY OF STOMACH CONTENTS
        SVIS=-0.25*FOSC+1.0
C STOMACH FILLING MULTIPLIER
        SFM=5.3E-8*H2O2
        IF(SFM.GE.2.65E-7) SFM=2.65E-7
        IF(SFM.LE.0.0) SFM=0.0
        SFM1=CH2O2*SFM
C STOMACH EMPTYING TO INTESTINE
        KH2O2=13.094E-6*SOSM1+0.00143
        IF(SOSM1.GE.171.0) KH2O2=-19.605E-6*SOSM1+0.0070214
        IF(SOSM1.GE.300.0) KH2O2=-5.273E-7*SOSM1+0.001298
        IF(KH2O2.LE.0.00085) KH2O2=0.00085

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      KH2O2=KH2O2/2.0
      IF(PHASE.EQ.0.0) KH2O2=KH2O2*3.43
C VISCOSITY INFLUENCE ON STOMACH EMPTYING
      KH2O3=KH2O2*SVIS
      IF(KH2O3.LE.0.1E-30) KH2O3=0.0
C INTESTINE SYSTEM
C INT. CARBOHYDRATE T/O
      CAI1=CAS4-CAIG
      IF(CAI1.LE.0.0) GO TO 690
      IF(CAI1.GE.0.1E-30) GO TO 700
690   IF(CAI1.LE.-0.1E-30) GO TO 700
      CAI1=0.0
700   CAI2=CAI1*0.99
      CAI3=CAI3+CAI2
      IF(CAI3.LE.0.1E-30) CAI3=0.0
      KCA=0.0004*4.0
      IF(PHASE.EQ.1.0) KCA=0.000264*4.0
      CAIK=CAI3/IVOL*KCA
      CAIG=SQRT(CAI3)*CAIK
C INT. FAT T/O
      FAI1=FAS4-FAIG
      IF(FAI1.LE.0.0) GO TO 710
      IF(FAI1.GE.0.1E-30) GO TO 720
710   IF(FAI1.LE.-0.1E-30) GO TO 720
      FAI1=0.0
720   FAI2=FAI1*0.95
      FAI3=FAI3+FAI2
      IF(FAI3.LE.0.1E-30) FAI3 = 0.0
      KFA=0.00028*4.0
      IF(PHASE.EQ.1.0) KFA=KFA*0.66
      FAIK=FAI3/IVOL*KFA
      FAIG=SQRT(FAI3)*FAIK
C INT. PROTEIN T/O
      PRI1=PRS4-PRIAA
      IF(PRI1.LE.0.0) GO TO 730
      IF(PRI1.GE.0.1E-30) GO TO 740
730   IF(PRI1.LE.-0.1E-30) GO TO 740
      PRI1=0.0
740   PRI2=PRI1*0.92
      PRI3=PRI3+PRI2
      IF(PRI3.LE.0.1E-30) PRI3=0.0
      KPRI=0.0004*4.0
      IF(PHASE.EQ.1.0) KPRI=KPRI*0.66
      PRIK=PRI3/IVOL*KPRI
      PRIAA=SQRT(PRI3)*PRIK
C INT. T/O OF INDIGESTIBLES
      INDI1=INDS4-INDI3
      IF(INDI1.LE.0.0) GO TO 750
      IF(INDI1.GE.0.1E-30) GO TO 760
750   IF(INDI1.LE.-0.1E-30) GO TO 760
      INDI1=0.0
760   INDI2=INDI2+INDI1
      IF(INDI2.LE.0.1E-30) INDI2=0.0
      INDI3=INDI2/(43200.0/4.0)
      IF(INDI2.GT.100.0) GO TO 10000
C TOTAL INTESTINE VOLUME
      IVOL=IH2O3+INDI2+CAI3+FAI3+PRI3+((KI3+NACLI1)/1000.-
0)

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IF(IVOL.LE.0.1) IVOL=0.1
C INTESTINE NACL
  NAI1=NAS4*0.98
  NAI2=NAI1-NAI4
  NAI3=NAI3+NAI2
  CLI1=CLS4*0.98
  CLI2=CLI1-CLI5
  CLI3=CLI3+CLI2
  NACLI1=NAI3+CLI3
  NACLI2=NACLI1/IH2O3
  NACLI3=NACLI2*614.179
  NACLI4=NACLI3-VOP3
  NACLI5=NACLI4*0.01
  IF(IH2O3.LE.1.0) NACLI5=NACLI4*(0.01*IH2O3)
  NACLI6=NACLI5/614.179
  NACLI7=NACLI2*0.000928
  IF(IH2O3.LE.1.0) NACLI7=NACLI2*(0.000232*IH2O3)
  NACLI8=NACLI6+NACLI7
  CLI4=CLI3/NACLI1
  CLI5=NACLI8*CLI4
  NAI4=NACLI8-CLI5
C INTESTINE POTASSIUM
  KI1=KS4*0.98
  KI2=KI1-KI8
  KI3=KI3+KI2
  KI4=KI3/IH2O3
  KI5=KI4*459.05371
  KI6=KI5-KS7
  KI7=KI6*0.01
  KI8=KI7*0.001
C INTESTINE H2O
  IH2O6=-0.086835*KI8
  IH2O1=H2O3*0.98
  FWAT=H2O3*0.02
  IH2O4=NACLI7*0.11628
  IH2O5=-0.11628*NACLI6
C LAST INFLUENCE IS NON-SPECIFIC ACTIVE H2O TRANSPORT
C REMOVES 5% INT. WATER/ MINUTE.
  IH2O7=IH2O6+IH2O5+IH2O4
  IF (IH2O3.GE.0.5) IH2O7=IH2O7+(IH2O3*0.0008333)
  IH2O2=IH2O1-IH2O7
  IH2O3=IH2O3+IH2O2
  IF(IH2O3.LE.0.1E-30) IH2O3=0.1E-30
C FOOD/ ENERGY METABOLISM
C DIETARY CARB ENERGY
  CAE=CAIG*3690.0*0.73685
C DIETARY FAT ENERGY
  FAE=FAIG*9300.0*0.73685
C DIETARY PROTEIN ENERGY
  PRE=PRIAA*4100.0*0.73685
C DIETARY ENERGY
  EIN=CAE+FAE+PRE
C METABOLIC RATE
  IF(PHASE.EQ.0.0) MR=0.6667
  IF(PHASE.EQ.1.0) MR=0.58333
C NET ENERGY SUPPLY/DEFICIT
  EIN1=EIN-MR
  IF(EIN1.GT.0.0) GO TO 155
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      IF(GLY.LE.0.0) EH205=0.0
      IF(GLY.LE.0.0) GLY1=0.0
      IF(GLY.LT.0.0) GO TO 160
      GO TO 157
155    IF(GLY.LE.0.0) GO TO 157
      IF(GLY.GT.0.35) GO TO 160
C GLYCOGEN T/O
157    GLY1=EIN1/3690.0
      EH205=GLY1*4.0
C TOTAL GLYCOGEN
      GLY=GLY+GLY1
C FAT T/O
160    IF(FAT.LE.0.0) EH207=0.0
      IF(FAT.LE.0.0) FAT1=0.0
      IF(FAT.LE.-0.1E-3) GO TO 170
      EIN3=EIN1*0.8
C FAT DE-/REPLETION RATE
      FAT1=EIN3/9000.0
      EH207=FAT1*1.07
C TOTAL FAT
      FAT=FAT+FAT1
C PROTEIN T/O
      EIN2=EIN1*0.2
170    IF(FAT.LE.0.0) EIN2=EIN1
C PROTEIN DE-/REPLETION RATE
      PR1=EIN2/4100.0
      EH206=PR1*3.27
C TOTAL PROTEIN
      PR=PR+PR1
C MET. WATER FROM ENERGY RE-/ DEPLETION
      EH208=EH205+EH206+EH207
C BODY FLUID WEIGHT
      FW=H2O2+IH2O3+PV+IFV+ICCV
C BODY WEIGHT
      WEIGHT=GLY+FAT+PR+FW+30.0
C PLASMA NA+ T/O
      DPNA=NAI4+NAS6+DIFNA1-DPNA1-UONA
      IF(DPNA.LE.0.0) GO TO 950
      IF(DPNA.GE.0.1E-30) GO TO 960
950    IF(DPNA.LE.-0.1E-30) GO TO 960
      DPNA=0.0
960    PNA=PNA+DPNA
      PCNA=PNA/PV
      DPNA1=PCNA*0.04774
C PLASMA CL- T/O
      DPCL=CLI5+CLS6+DIFCL1-DPCL1-UOCL
      IF(DPCL.LE.0.0) GO TO 970
      IF(DPCL.GE.0.1E-30) GO TO 980
970    IF(DPCL.LE.-0.1E-30) GO TO 980
      DPCL=0.0
980    PCL=PCL+DPCL
      PCCL=PCL/PV
      DPCL1=PCCL*0.05
C PLASMA K+ T/O
      DPK=KI8+KS9+DIFK1-DPK1-UOK
      IF(DPK.LE.0.0) GO TO 990
      IF(DPK.GE.0.1E-30) GO TO 1000
990    IF(DPK.LE.-0.1E-30) GO TO 1000
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      DPK=0.0
1000  PK=PK+DPK
      PCK=PK/PV
      DPK1=PCK*0.047
C INDIVIDUAL ION OSMOLALITIES,mOsmole/litre
      PCNA1=PCNA*1000.0/23.0
      PCCL1=PCCL*1000.0/35.45
      PCK1=PCK*1000.0/39.1
      NACL1=PCNA1+PCCL1
C PLASMA OSMOLALITY,mOsmoles/litre
      POSM=PCNA1+PCCL1+PCK1+PCCA1+PCHCO3+PCG
C PLASMA OSMOTIC PRESSURE (19.3*0.93 CORRECTION),mmHg
      POP=POSM*17.949
C FOR WANT OF A BETTER NAME, NEURAL INTRACELLULAR SYSTEM.
C      ***** WATER METABOLISM
      NCO1SM=NCNA*43.4763+NCK*25.575+NCCL*28.209+(93.96*-
(.05/NV))+47
      NCO1SM=NCO1SM+ICG
      PO1SM=PCNA*43.4763+PCK*25.575+PCCL*28.209+PCG+27+5-
.6
      NV=NV+((NCO1SM-PO1SM)*1.666E-5)
C      ***** GLUCOSE METABOLISM
      ICG=IG/NV
      GUTIL=NCNAO*3.0+NSKIN*3.0
      IG=IG+(((PCG-ICG)*.001)-GUTIL)
      IF(IG.LT.0.01) IG=0.01
C      ***** SODIUM METABOLISM
      NCNAIN=(PCNA-NCNA)*.0003543
      NCNAO1=NCNA*.005
      NCNAO2=NCNAO1
      IF(PCK.LT.0.25 ) NCNAO2=NCNAO1*(PCK/0.1645)
      IF(PCK.GE.0.25) NCNAO2=NCNAO1*(0.25/0.1645)
      NCNAO3=NCNAO2
      I1G=I1G+((ICG-I1G)*.1)
      IF(I1G.LT. 1.5 ) NCNAO3=NCNAO2*(I1G/1.5)
      NCNAO4=0.0
      IF(NCNA .GT. 0.199705 ) NCNAO4=(NCNA-0.199705)*.005
      NCNAO=NCNAO3+NCNAO4
      NNA=NNA+(NCNAIN-NCNAO)
      NCNA=NNA/NV
C      ***** POTASSIUM METABOLISM
C      NON-SPECIF(IC POTASSIUM TRANSPORT
      NSKIN=0.0
      IF(PCK.GE.0.2) NSKIN=(PCK-0.2)*.05
      IF(I1G.LT. 4.0 ) NSKIN=NSKIN*(I1G/4.0)
      NK=NK+(((NSKIN+(NCNAO3*1.13333))-((NCK-
PCK)*2.11645E-4)))
      NCK=NK/NV
C INTERSTITIAL FLUID NA+ T/O
      DIFNA=DPNA1-DIFNA1-DICNA
      IF(DIFNA.LE.0.0) GO TO 1010
      IF(DIFNA.GE.0.1E-30) GO TO 1020
1010  IF(DIFNA.LE.-0.1E-30) GO TO 1020
      DIFNA=0.0
1020  IFNA=IFNA+DIFNA
      IFCNA=IFNA/IFV
      DIFNA1=IFCNA*0.05
C INTERSTITIAL FLUID CL

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DIFCL=DPCL1-DIFCL1-DICCL
IF(DIFCL.LE.0.0) GO TO 1030
IF(DIFCL.GE.0.1E-30) GO TO 1040
1030 IF(DIFCL.LE.-0.1E-30) GO TO 1040
DIFCL=0.0
1040 IFCL=IFCL+DIFCL
IFCCL=IFCL/IFV
DIFCL1=IFCCL*0.047236
C INTERSTITIAL FLUID K+ T/O
DIFK=DPK1-DIFK1-DICK
IF(DIFK.LE.0.0) GO TO 1050
IF(DIFK.GE.0.1E-30) GO TO 1060
1050 IF(DIFK.LE.-0.1E-30) GO TO 1060
DIFK=0.0
1060 IFK=IFK+DIFK
IFCK=IFK/IFV
DIFK1=IFCK*0.05
C INT. FLUID INDIVIDUAL ION OSMOLALTIES,mOsmoles/l
IFCNA1=IFCNA*1000.0/23.0
IFCCL1=IFCCL*1000.0/35.45
IFCK1=IFCK*1000.0/39.1
C INT. FLUID OSMOLALITY,mOsmole/l
IFOSM=IFCNA1+IFCCL1+IFCK1+IFHCO3+PCG+PCCA1
C INT. FLUID OSMOTIC PRESSURE,mmHg.
IFOP=IFOSM*17.949
C INTRACELLULAR K+ T/O
DICK1=IFCK*0.08721
DICK2=ICCK*0.0025
DICK=DICK1-DICK2
IF(DICK.LE.0.0) GO TO 1070
IF(DICK.GE.0.1E-30) GO TO 1080
1070 IF(DICK.LE.-0.1E-30) GO TO 1080
DICK=0.0
1080 ICCK=ICCK+DICK
ICCK=ICCK/ICCV
ICCK1=ICCK*1000.0/39.1
C INTRACELLULAR CL
DICCL1=IFCCL*0.0025
DICCL2=ICCK*0.06385
DICCL=DICCL1-DICCL2
IF(DICCL.LE.0.0) GO TO 1090
IF(DICCL.GE.0.1E-30) GO TO 1100
1090 IF(DICCL.LE.-0.1E-30) GO TO 1100
DICCL=0.0
1100 ICCL=ICCL+DICCL
ICCL=ICCL/ICCV
ICCL1=ICCL*1000.0/35.45
C INTRACELLULAR NA+
DICNA1=IFCNA*0.0025
DICNA2=ICNA*0.035325
DICNA=DICNA1-DICNA2
IF(DICNA.LE.0.0) GO TO 1110
IF(DICNA.GE.0.1E-30) GO TO 1120
1110 IF(DICNA.LE.-0.1E-30) GO TO 1120
DICNA=0.0
1120 ICNA=ICNA+DICNA
ICNA=ICNA/ICCV
ICNA1=ICNA*1000.0/23.0
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C INTRACELLULAR OSMOLARITY
  ICOSM1=ICCK1+ICCL1+ICCN1+ICORG+MG+ICHCO3+ICHPO
  ICOSM2=ICOSM1*0.93
C INTRACELLULAR O.P.
  ICOP=ICOSM2*19.3
C THIS DETERMINES WATER FLOW W.R.T. OSMOTIC PRESSURE
  GRADIENT
  ICCV4=(ICOSM1-IFOSM)*0.0041667
C THIS INTEGRATES O.P. INDUCED WATER FLOW, TO GIVE TOTAL
  O.P. FLOW
  TICCV4=TICCV4+ICCV4
C INTRACELLULAR VOLUME, COMPRISED OF O.P. FLOW AND WATER
  ACCOMPANYING
C ENERGY STORES IN APPROPRIATE PROPORTIONS
  ICCV=TICCV4+(GLY*4.0)+(FAT*1.07)+(PR*3.27)
C THIS DETERMINES TOTAL CELLULAR FLUID FLOW RATE, DUE TO
  O.P. AND ENERGY
C STORE DEPLETION/REPLETION
  ICCV1=EH2O8+ICCV4
C ALDOSTERONE CONTROL
C PLASMA K+ INFLUENCE
  IF (PCK.LE.0.155) ALD1= PCK*0.141935
  IF (PCK.GE.0.155) ALD1= 1.41935*PCK-0.198
  IF(ALD1.GT.0.1) ALD1=0.1
  IF (ALD1.LE.0.0) ALD1=0.0
C ANGIOTENSIN II INFLUENCE
  ALD2=0.1875*ANGII
  IF (ANGII.GE.0.028) ALD2=4.875*ANGII-0.13125
  IF (ALD2.LE.0.0) ALD2=0.0
  IF (ALD2.GE.0.1) ALD2=0.1
  ALD6=ALD1+ALD2
  ALD7=ALD6-ALD10
  IF(ALD7.LE.0.0) GO TO 1170
  IF(ALD7.GE.0.1E-30) GO TO 1180
1170 IF(ALD7.LE.-0.1E-30) GO TO 1180
  ALD7=0.0
1180 ALD8=ALD8+ALD7
  ALD9=ALD8*0.0002143
  ECFV=PV+IFV
  ALD=ALD8/ECFV
  ALD11=ALD*GFR
  ALD10=ALD9+ALD11
  ALD15=ALD-ALD16
  IF(ALD15.LE.0.0) GO TO 1190
  IF(ALD15.GE.0.1E-30) GO TO 1200
1190 IF(ALD15.LE.-0.1E-30) GO TO 1200
  ALD15=0.0
1200 ALD17=ALD15/900.0
  ALD16=ALD16+ALD17
C RENIN CONTROL
C AUTONOMIC INFLUENCE ON RENIN
  RSR1=AM*0.0011636
  IF(AM.GE.0.935) RSR1=0.033473*AM-0.030209
C RIGHT ATRIAL PRESSURE INFLUENCE ON RENIN
  RSR2=-0.032746*RAP+0.1
  IF(RAP.GT.2.95) RSR2=-0.004624*RAP+0.017041
  IF(RAP.GT.3.45) RSR2=-0.000702*RAP+0.0035097
  IF(RAP.GE.5.0) RSR2=0.0

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C RENAL GLOMERULAR PRESSURE INFLUENCE ON RENIN
  RSR3=-0.00339*PGC+0.08663
  IF(PGC.GE.17.0) RSR3=-0.001353*PGC+0.052
  IF(PGC.GE.27.0) RSR3=-0.0007191*PGC+0.0348857
  IF(PGC.GE.47.0) RSR3=-0.72533E-4*PGC+4.4971E-3
  IF(PGC.GE.62.0) RSR3=0.0
C HENLE Na+ FLOW INFLUENCE ON RENIN
  RSR4=-1.2475E6*HNAL+0.05
  IF(HNAL.GT.0.3136E-7) RSR4=-3.12245E5*HNAL+0.02067
  IF(HNAL.GT.0.6272E-7) RSR4=-1.7347E4*HNAL+0.002176
  IF(HNAL.GE.1.2544E-7) RSR4= 0.0
C INHIBITION OF RENIN RELEASE BY K+
  KREN=-3.19956E7*HKL+1.12987
  IF(KREN.LE.0.0) KREN=0.0
  RSR5=RSR4*KREN
  RSR6=RSR1+RSR2+RSR3+RSR5
C ADH INHIBITION OF RENIN RELEASE
  ADHREN=1.0
  IF(ADH.GE.10.0) ADHREN=-0.025*ADH+1.25
  IF(ADH.GE.30.0) ADHREN=0.5
  RSR7=RSR6*ADHREN
C ANGIOTENSIN II INHIBITION OF RENIN RELEASE
  ANGREN=1.0
  IF(ANGII.GE.0.1) ANGREN=-0.75*ANGII+0.85
  IF(ANGII.GE.0.2) ANGREN=0.7
  RSR8=RSR7*ANGREN
C RENIN SECRETION RATE
  RSR9=RSR8-RSR
  IF(RSR9.LE.0.0) GO TO 360
  IF(RSR9.GE.0.1E-30) GO TO 370
360  IF(RSR9.LE.-0.1E-30) GO TO 370
      RSR9=0.0
370  RSR10=RSR9*0.04
      RSR=RSR+RSR10
      REN1=RSR-REN5
      IF(REN1.LE.0.0) GO TO 1210
      IF(REN1.GE.0.1E-30) GO TO 1220
1210  IF(REN1.LE.-0.1E-30) GO TO 1220
      REN1=0.0
1220  REN2=REN2+REN1
C PLASMA RENIN CONCENTRATION
  REN=REN2/PV
C HEPATIC BLOOD FLOW,ml/s
  HBF=0.0399*CO+0.03752
  IF(CO.LE.0.753) HBF=0.09942*CO-0.00727
C HEPATIC PLASMA FLOW,ml/s
  HPF=PVBV*HBF
C HEPATIC CLEARANCE OF RENIN
  HPF1=HPF*0.25
  REN5=REN*HPF1
C ANGIOTENSIN I CONTROL
  ANGI1=REN*0.003527
  ANGI2=ANGI1*PV
  ANGI3=ANGI2-ANGII1
  IF(ANGI3.LE.0.0) GO TO 1230
  IF(ANGI3.GE.0.1E-30) GO TO 1240
1230  IF(ANGI3.LE.-0.1E-30) GO TO 1240
      ANGI3=0.0

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1240   ANGI4=ANGI4+ANGI3
C PLASMA ANG I CONCENTRATION
      ANGI=ANGI4/PV
C CARDIAC PLASMA OUTPUT,ml/s
      CPO=CO*PVBV
C CONVERSION OF ANG I TO ANG II
      ANGI5=CPO*0.5
C ANGIOTENSIN II CONTROL
      ANGII1=ANGI*ANGI5
      ANGII2=ANGII1-ANGII4
      IF(ANGII2.LE.0.0) GO TO 1250
      IF(ANGII2.GE.0.1E-30) GO TO 1260
1250   IF(ANGII2.LE.-0.1E-30) GO TO 1260
      ANGII2=0.0
1260   ANGII3=ANGII3+ANGII2
      ANGII4=ANGII3*0.036
      ANGII=ANGII3/PV
C PLASMA COLLOID O.P. CONTROL
      DPPRF=PPRC*(-8.67D-7)+1.214D-7
      PPRG=DPLO+DPPRF
      DPPRL=PPRC/864000.0
      PPRL=DPLI+DPPRL
      NETPPR=PPRG-PPRL
      IF(NETPPR.LE.0.0) GO TO 1270
      IF(NETPPR.GE.0.1E-30) GO TO 1280
1270   IF(NETPPR.LE.-0.1E-30) GO TO 1280
      NETPPR=0.0
1280   PPR=PPR+NETPPR
      IF(PPR.LE.0.0)      PPR=0.0
      PVML=PV*1000.0
      PPRC=PPR/PVML
      IF(PPRC.LE.0.0)      PPRC=0.00001
      PCOP=PPRC**1.6*1767.03
C   STARLING CAPILLARY EQ.,MMHG
      CWP=CP+TCOP-PCOP-IFP
C   CAPILLARY PERMEABILITY, ML,S
      IF(CWP.GE.0.0) DIFVC=CWP*.0167
      IF(CWP.GE.0.0) GO TO 500
      IF(IFV.GE.117.0) DIFVC=CWP*0.0167
      IF(IFV.LE.117.0) DIFVC=CWP*0.000167
      IF(IFV.LE.113.0) DIFVC=CWP*0.0000167
      IF(IFV.LE.109.0) DIFVC=0.0
500    IF(DIFVC.GE.0.0) GO TO 10
      NA3=IFCNA*DIFVC
      CL3=IFCCL*DIFVC
      K5=IFCK*DIFVC
      GO TO 20
10     NA3=PCNA*DIFVC
      CL3=PCCL*DIFVC
      K5=PCK*DIFVC
20     IF(BV.GE.35.0) NA3=0.0
      IF(BV.GE.35.0) CL3=0.0
      IF(BV.GE.35.0) K5=0.0
C   INTERSTITIAL FLUID FLOW,ML/S
      DIFV=DIFVC-LF
      IF(DIFV.LE.0.0) GO TO 1290
      IF(DIFV.GE.0.1E-30) GO TO 1300
1290   IF(DIFV.LE.-0.1E-30) GO TO 1300

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      DIFV=0.0
C INT. FLUID VOL., MICROL THEN ML
1300 IFV=IFV+DIFV-ICCV1
      IF(IFV.LE.10.0) IFV=10.0
C IFV/IFP,MMHG
      IFP=0.07318*IFV-6.9521
      IF(IFV.GE.95.0) IFP=0.2*IFV-19.0
C IFP/LF,ML/S
      LF=0.0001923*IFP+0.001
      IF(IFP.GE.0.0) LF=0.001*IFP+0.001
      IF (IFV.LT.117.0) LF=LF*((IFV-112.0)*0.2)
      IF (LF.LE.0.0) LF=0.0
C INTERSTITIAL FLUID PROTEIN LOSS,MG/S
      DPLO=IFPRC*LF
C NET I.F. PROTEIN FLOW
      DPL=DPLI-DPLO
      IF(DPL.LE.0.0) GO TO 1310
      IF(DPL.GE.0.1E-30) GO TO 1320
1310 IF(DPL.LE.-0.1E-30) GO TO 1320
      DPL=0.0
C IFPR,MG
1320 IFPR=IFPR+DPL
      IF(IFPR.LE.0.0) IFPR=0.0
C I.F. PROTEIN CONC.,MG/ML
      IFVML=IFV*1000.0
      IFPRC=IFPR/IFVML
C TISSUE COLLOID OSMOTIC PRESSURE,MMHG
      TCOP=IFPRC**1.6*1767.03
C TRANSCAPILLARY O.P. GRADIENT
      GRCOP=PCOP-TCOP
      IF(GRCOP.LE.0.0) GO TO 1330
      IF(GRCOP.GE.0.1E-30) GO TO 1340
1330 IF(GRCOP.LE.-0.1E-30) GO TO 1340
      GRCOP=0.0
C PROTEIN FLOW INTO INTERSTITIAL FLUID
1340 DPLI=GRCOP/2500000.0
C PLASMA VOLUME CHANGE RATE,ML/S
      DPV=H2O4+IH2O7-DIFV-UO-IWL
      IF(DPV.LE.0.0) GO TO 1350
      IF(DPV.GE.0.1E-70) GO TO 1360
1350 IF(DPV.LE.-0.1E-30) GO TO 1360
      DPV=0.0
C PLASMA VOLUME,ML
1360 PV=PV+DPV
      IF(PV.LE.0.0) PV=0.001
      IF(PV.GE.30.0) PV=30.0
C BLOOD VOLUME,ML
      BV=PV+RBCV
      IF(BV.LE.0.0) BV=0.0
      IF(BV.GE.35.0) BV=35.0
C PRESSURE GRADIENT
      DIFF=MSP-RAP
C BLOOD VOLUME/MEAN SYSTEMIC PRESSURE,MMHG
      MSPC=1.692*BV-25.334
      IF(BV.LE.18.095) MSPC=0.7338*BV-7.9958
      IF(BV.LE.10.896) MSPC=0.0
C AM INFLUENCE ON MSP
      MSP=MSPC*AM

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C CARDIAC OUTPUT, ML/S
  CO=DIFF/RVR
  IF(CO.LE.0.0) CO=0.0
C SYSTEMIC PRESSURE GRADIENT
  IF(CO.GE.10.0) CO=10.0
  APRAP=TPR*CO
C ARTERIAL PRESSURE,MMHG
  AP=APRAP+RAP
C ARTERIAL PRESSURE MULTIPLIER
  APMULT=1.0
  IF(AP.GE.150.0) APMULT=1.0-(0.00004*(AP-150)**2)
  IF(AP.GE.300.0) APMULT=0.1
C HEART EFFICIENCY
  CON=CO/CM
C CON/RIGHT ATRIAL PRESSURE,MMHG
  IF(CON.GE.10.0) CON=10.0
  RAP=CON**2-1.21*0.83083
  IF(CON.LE.0.0) RAP=-1.0
  IF(RAP.GE.10.0) RAP=10.0
C ARTERIAL RESISTANCE, P R UNITS
  ANGIIR=0.0
  IF(ANGII.GE.0.02723) ANGIIR=3.6724*ANGII-0.1
  IF(ANGII.GE.0.16338) ANGIIR=0.3531*ANGII+0.4423
  IF(ANGIIR.GE.0.7954) ANGIIR=0.7954
  AMR=(AM+ANGIIR)/2.0
C ARTERIAL PRESSURE GRADIENT,MMHG
  PGART=CO*AR
C CAPILLARY PRESSURE,MMHG
  CP=AP-PGART
C VASCULARITY CONTROL
  TCO=TCO+(CO-0.1)
  IF(T.LT.60.0) GO TO 3690
  MEANCO=TCO/T
  TCO=0.0
  DVASF1=18.0
  IF(MEANCO.GT.0.72)
DVASF1=18.0-(MEANCO-0.72)**2*28.929
  DVASF=DVASF1/10.0**4
  IF(MEANCO.GT.1.5088) DVASF=0.0
  DVASt=DVASF-DVASD
  VAS=VAS+DVASt
  DVASD=VAS*0.0003
  BAR=KBAR/VAS
3690  AR=AMR*BAR
      TPR=AR+VR
      RVR=(8.0*VR+AR)/40.0
C AUTONOMIC CONTROL
C CNS ISCHAEMIC RESPONSE
  IF(CO.LE.0.8) CBF=CO*0.0161
  IF(CO.GT.0.8) CBF=0.00183*CO+0.01143
  AMCNS1=0.0
  IF(CBF.LE.0.006) AMCNS1= -50.0*CBF+0.3
  IF(CBF.LE.0.004) AMCNS1= -225.0*CBF+1.0
C STIM/RESPONSE LATENCY
  AMCNS2=AMCNS1-AMCNS4
  IF(AMCNS2.LE.0.0) GO TO 380
  IF(AMCNS2.GE.0.1E-30) GO TO 390
380  IF(AMCNS2.LE.-0.1E-30) GO TO 390

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      AMCNS2=0.0
390   IF(AMCNS2.LE.-0.6) AMCNS2=-0.6
      AMCNS3=AMCNS2/10.0
      AMCNS4=AMCNS4+AMCNS3
      AMCNS=AMCNS4-AMCNS7
C   AMCNS ADAPT CONTROL
      IF(T.LT.60.0) GO TO 5200
      AMCNS5=AMCNS/6100.0
      AMCNS8=AMCNS7/18300.0
      AMCNS9=AMCNS1
      IF(AMCNS9.LE.0.01) AMCNS9=0.01
      AMCN10=AMCNS8/AMCNS9
      AMCNS6=AMCNS5-AMCN10
      IF(AMCNS6.LE.0.0) GO TO 1370
      IF(AMCNS6.GE.0.1E-30) GO TO 1380
1370  IF(AMCNS6.LE.-0.1E-30) GO TO 1380
      AMCNS6=0.0
1380  AMCNS7=AMCNS6+AMCNS7
C   CAROTID BARORECEPTOR RESPONSE
5200  AMCAR1=0.85
      IF(AP.GT.50.0) AMCAR1=-0.0004348*AP+0.87174
      IF(AP.GT.73.0) AMCAR1=-0.01595*AP+2.004
      IF(AP.GT.131.0)AMCAR1=-0.001707*AP+0.32366
      IF(AP.GT.172.0)AMCAR1=-0.001071*AP+0.21429
      IF(AP.GT.200.0)AMCAR1=0.0
C   STIM/RESPONSE LATENCY
      AMCAR2=AMCAR1-AMCAR
      IF(AMCAR2.LE.0.0) GO TO 400
      IF(AMCAR2.GE.0.1E-30) GO TO 410
400   IF(AMCAR2.LE.-0.1E-30) GO TO 410
      AMCAR2=0.0
410   AMCAR3=AMCAR2*0.15
      AMCAR=AMCAR+AMCAR3
C   AORTIC BARORECEPTOR RESPONSE
      AMAOR1=0.45
      IF(AP.GT.103.0)  AMAOR1=-0.075*AP+8.175
      IF(AP.GT.105.0)  AMAOR1=-0.03*AP+3.45
      IF(AP.GT.110.0)  AMAOR1=-0.006667*AP+0.88333
      IF(AP.GT.125.0)  AMAOR1=-0.001515*AP+0.2394
      IF(AP.GT.158.0)  AMAOR1=0.0
C   STIM/RESPONSE LATENCY
      AMAOR2=AMAOR1-AMAOR
      IF(AMAOR2.LE.0.0) GO TO 420
      IF(AMAOR2.GE.0.1E-30) GO TO 430
420   IF(AMAOR2.LE.-0.1E-30) GO TO 430
      AMAOR2=0.0
430   AMAOR3=AMAOR2*0.1
      AMAOR=AMAOR+AMAOR3
C   VENOUS STRETCH RECEPTOR INFLUENCE ON AM
      RAP1=RAP+0.5
      AMVEN1=1.5
      IF(RAP1.GE.-0.1)  AMVEN1=-0.2564*RAP1+1.47436
      IF(RAP1.GE.1.85)  AMVEN1=-0.43478*RAP1+1.80435
      IF(RAP1.GE.3.0)   AMVEN1=-0.16234*RAP1+0.98701
      IF(RAP1.GE.4.54)  AMVEN1=-0.051862*RAP1+0.48545
      IF(AMVEN.LE.0.0) AMVEN1=0.0
C   STIM/RESPONSE LATENCY
      AMVEN2=AMVEN1-AMVEN

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AMVEN3=AMVEN2*0.1
IF(AMVEN3.LE.0.0) GO TO 510
IF(AMVEN3.GE.0.1E-30) GO TO 520
510  IF(AMVEN3.LE.-0.1E-30) GO TO 520
      AMVEN3=0.0
520  AMVEN=AMVEN+AMVEN3
C BARORECEPTOR ADAPTATION
AMBAR1=AMCAR+AMAOR+AMVEN
IF(T.LT.60) GO TO 5490
AMBAR2=AMBAR1*AMBAR7
AMBAR3=AMBAR2/257.0
AMBAR4=-1.0*AMBAR3+.7
AMBAR5=AMBAR4-AMBAR3
IF(AMBAR5.LE.0.0) GO TO 1390
IF(AMBAR5.GE.0.1E-30) GO TO 1400
1390 IF(AMBAR5.LE.-0.1E-30) GO TO 1400
      AMBAR5=0.0
1400 AMBAR6=AMBAR6+AMBAR5
      IF(AMBAR6.GT.13.0) AMBAR6=13.0
      AMBAR7=1.0
      IF(AMBAR6.LT.5.0) AMBAR7=AMBAR6/5.0
5490 AMBAR=AMBAR1*AMBAR7
C CHEMORECEPTOR INFLUENCES
CBPG=AP/200.0
CBR=30.0
CBBF=CBPG/CBR
AMCHE1=0.6
IF(CBBF.GT.0.0042)  AMCHE1=-70.0*CBBF+0.894
IF(CBBF.GT.0.0062)  AMCHE1=-55.263*CBBF+0.8026
IF(CBBF.GT.0.01)    AMCHE1=-32.0*CBBF+0.57
IF(CBBF.GT.0.0125)  AMCHE1=-16.667*CBBF+0.3783
IF(CBBF.GT.0.0167)  AMCHE1=-1.2712*CBBF+0.1212
C STIM/RESPONSE LATENCY
AMCHE2=AMCHE1-AMCHE4
IF(AMCHE2.LE.0.0) GO TO 440
IF(AMCHE2.GE.0.1E-30) GO TO 450
440  IF(AMCHE2.LE.-0.1E-30) GO TO 450
      AMCHE2=0.0
450  AMCHE3=AMCHE2*0.2
      AMCHE4=AMCHE4+AMCHE3
C CHEMORECEPTOR ADAPT
AMCHE=AMCHE4-AMCHE8
IF(T.LT.60.0) GO TO 5700
AMCHE5=AMCHE-0.1
AMCHE6=AMCHE5/6000.0
IF(AMCHE4.LE.0.1) AMCH10=0.1
IF(AMCHE4.GE.0.1) AMCH10=AMCHE4
AMCHE9=AMCHE8/12000.0
AMCH11=AMCHE9/AMCH10
AMCHE7=AMCHE6-AMCH11
IF(AMCHE7.LE.0.0) GO TO 1410
IF(AMCHE7.GE.0.1E-30) GO TO 1420
1410 IF(AMCHE7.LE.-0.1E-30) GO TO 1420
      AMCHE7=0.0
1420 AMCHE8=AMCHE8+AMCHE7
C AM SUMMATION
5700 AM1=AMCNS+AMCHE+AMBAR
C ISCHAEMIA CIRCUIT

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ISC1=0.0
IF(CBF.LE.0.0106)  ISC1=-0.6383*CBF+0.00678
ISC3=0.0
IF(ISC5.GT.1.0)  GO TO 5770
IF(CBF.GE.0.01)  ISC3=CBF*0.4175-0.004175
IF(CBF.GE.0.014) ISC3=0.00167
5770  ISC4=ISC3*ISC5
      ISC2=ISC4-ISC1
      ISC5=ISC5+ISC2
      IF(ISC5.GT.1.0) ISC5=1.0
      IF(ISC5.LE.0.0) ISC5=0.0
      AM=AM1*ISC5
C CARDIAC MULTIPLIER
      CM=(AM-AMCHE)*APMULT
C DRINKING DECISION SYSTEM
C CALIBRATION OF INDIVIDUAL STIMULI
C INTRACELLULAR STIMULUS (NEURAL INTRACELLULAR 'GLUCOSE'
CONCENTRATION)
      INIC=-36.49*ICG+103.29
      IF(INIC.LE.0.0) INIC=0.0
C REMOVE INTRACELLULAR STIMULUS ON DAY 3
C VOLEMIC STIMULUS (RIGHT ATRIAL PRESSURE)
      INRAP=-1.0*RAP+12.5
      IF(RAP.LE.2.5) INRAP=-4.0*RAP+20.0
      IF(INRAP.GE.15.0) INRAP=15.0
C ANGIOTENSIN STIMULUS
      INANG=100.0*ANGII+5.0
      INANG=INANG+3.0
      IF(INANG.GE.15.0) INANG=15.0
      IF(INANG.LE.9.0) INANG=9.0
C INHIBITION/ ADDITION SYSTEM
      INIC1=INIC*0.22
      INRAP1=INRAP*0.22
      INANG1=INANG*0.22
      INIC2=INIC-(INRAP1+INANG1)
      IF(INIC2.LE.0.0) INIC2=0.0
      INRAP2=INRAP-(INIC1+INANG1)
      IF(INRAP2.LE.0.0) INRAP2=0.0
      INANG2=INANG-(INIC1+INRAP1)
      IF(INANG2.LE.0.0) INANG2=0.0
      TOTIN=INIC2+INRAP2+INANG2
      H2OIN=0.0
      IF(TOTIN-IH2O3.GT.24.0) H2OIN=0.03
      IF (INIC.LE.5.0) H2OIN=0.0
C THIS PREVENTS DRINKING AFTER DAY 1
C
      IF(COUNT.GT.4320.0.AND.COUNT.LE.5760.0) H2OIN=0.0
      IF(T.EQ.60.0) T=0.0
      T=T+1.0
      S=S+1.0
      IF(S.LT.60.0) GO TO 100
      S=0.0
      M=M+1.0
C THIS SYSTEM DECIDES WHEN THE ANIMAL IS TO BE FED.
C ALSO COUNTS, FOR TIMING EXPERIMENTS ETC.
      COUNT=COUNT+1.0
      MC=MC+1.0
      IF(MC.LT.60.0)  GO TO 120
      IF(MC.LE.90.0)  GO TO 130

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IF(MC.LT.150.0) GO TO 120
IF(MC.LE.188.0) GO TO 130
IF(MC.LT.240.0) GO TO 120
IF(MC.LE.288.0) GO TO 130
IF(MC.LT.600.0) GO TO 120
IF(MC.LE.609.0) GO TO 140
IF(MC.LT.870.0) GO TO 120
IF(MC.LE.879.0) GO TO 140
IF(MC.LT.1020.0) GO TO 120
IF(MC.LE.1030.0) GO TO 140
IF(MC.LT.1140.0) GO TO 120
IF(MC.LE.1164.0) GO TO 130
IF(MC.LT.1200.0) GO TO 120
IF(MC.LE.1230.0) GO TO 130
IF(MC.LT.1290.0) GO TO 120
IF(MC.LE.1318.0) GO TO 130
IF(MC.LT.1410.0) GO TO 120
IF(MC.LE.1437.0) GO TO 130
120 FOODIN=0.0
GO TO 150
130 FOODIN=0.0012
GO TO 150
140 FOODIN=0.0014
150 IF(MC.EQ.1440.0) MC=0.0
C THIS SYSTEM BREAKS THE FOODIN RATE DOWN TO DIETARY
CONSTITUENTS
C IF(COUNT.GE.4320.0.AND.COUNT.LE.5760.0)
FOODIN=0.0001
C IF(COUNT.GT.5760.0) FOODIN=0.0
NAIN=FOODIN*1000.0*0.0035
CLIN=FOODIN*1000.0*0.003
KIN=FOODIN*1000.0*0.0015
PRIN=FOODIN*0.21
CARIN=FOODIN*0.48
FATIN=FOODIN*0.05
INDIN=FOODIN*0.176
FH2OIN=FOODIN*0.06
C IF(COUNT.GE.5760.0) GO TO 10000
IF(M.LT.60.0) GO TO 100
M=0.0
H=H+1.0
10000 WRITE(6,6100) H,M,COUNT,CO,AP
WRITE(6,6200) AM,RAP,BV,PCNA1
WRITE(6,6300) H2O2,IH2O3,SVOL,IVOL
WRITE(6,6400) IWL,H2OIN,CP,IFV
WRITE(6,6500) PCK,ANGII,ALD1,ALD2
WRITE(6,6493) GLY,FAT,PR,MR
WRITE(6,6494) EIN,EIN1,FW,WEIGHT
WRITE(6,6495) ICCV,ICCV4,EH2O4,EH2O8
WRITE(6,6496) IFOP,ICOP,ICCK,ICCNA
WRITE(6,6499) HH2OIN,HFIN,CNARF,ALD16
WRITE(6,6510) HUO,HUONA,HUOCL,HUOK
WRITE(6,6520) HIWL,HSTOM,HINT
WRITE(6,6580) INIC
WRITE(6,6585) INRAP,INANG,INIC2
WRITE(6,6590) INRAP2,INANG2,TOTIN
WRITE(6,6592) NCO1SM,PO1SM,NV,ICG
WRITE(6,6595) NCNA,NCCL,NCK

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        WRITE(6,9000)
        IF(COUNT.GT.6060.0) GO TO 1
        IF(H.LT.24.0) GO TO 5885
        H=0.0
        D=D+1.0
5885    IF(H.LT.6.0) GO TO 5905
        IF(H.GE.18.0) GO TO 5905
        PHASE=1.0
        GO TO 100
5905    PHASE=0.0
        GO TO 100
1       STOP
6100                                FORMAT(1H
, 'H',F9.1,'M',F9.1,'COUNT',F9.1,'CO',E15.4,'AP',E15.4)
6200                                FORMAT(1H      , 'AM',E15.4,'      RAP',E15.4,'
EV',E15.4,'PCNA1',E15.4)
6300                                FORMAT(1H      , 'H2O2',E15.4,'
IH2O3',E15.4,'SVOL',E15.4,'IVOL',E15.4)
6400                                FORMAT(1H , 'IWL',E15.4,' H2OIN',E15.4,' CP',E15.4,'
IPV',E15.4)
7500                                FORMAT(1H
, 'PCK',E15.4,'ANGII',E15.4,'ALD1',E15.4,'ALD2',E15.4)
8493                                FORMAT(1H
, 'GLY',E15.4,'FAT',E15.4,'PR',E15.4,'MR',E15.4)
8494                                FORMAT(1H
, 'EIN',E15.4,'EIN1',E15.4,'FW',E15.4,'WEIGHT',E15.4)
8495                                FORMAT(1H
, 'ICCV',E15.4,'ICV4',E15.4,'EH2O4',E15.4,'EH2O8',E15.4)
8496                                FORMAT(1H
, 'IFOP',E15.4,'ICOP',E15.4,'ICCK',E15.4,'ICCNA',E15.4)
8499                                FORMAT(1H
, 'HH2OIN',E15.4,'HFIN',E15.4,'CNF',E15.4,'ALD16',E15.4)
8510                                FORMAT(1H
, 'HUO',E15.4,'HUONA',E15.4,'HUOCL',E15.4,'HUOK',E15.4)
8520                                FORMAT(1H , 'HIWL',E15.4,'HSTOM',E15.4,'HINT',E15.4)
8580                                FORMAT(1H , 'INIC',E15.4)
8585                                FORMAT(1H
, 'INRAP',E15.4,'INANG',E15.4,'INIC2',E15.4)
8590                                FORMAT(1H
, 'INRAP2',E15.4,'INANG2',E15.4,'TOTIN',E15.4)
8592                                FORMAT(1H
, 'NCO1SM',E15.4,'PO1SM',E15.4,'NV',E15.4,'ICG',E15.4)
8595                                FORMAT(1H , 'NCNA',E15.4,'NCCL',E15.4,'NCK',E15.4)
9000                                FORMAT(1H
, '*****')
        END

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